ARTHRITIS DRUGS ADVISORY COMMITTEE MEETING

2/4-5/97

Agenda

Arthritis Advisory Committee
Food and Drug Administration
Center for Drug Evaluation and Research

February 4, 1997
Gaithersburg Hilton
620 Perry Parkway, Gaithersburg, MD.

NDA 50-735, Neoral®, (cyclosporine) Sandoz

Open Session

8:30 Call to Order, Introductions: Michelle Petri, M.D., Chair
Meeting Statement: Kathleen Reedy, Executive Secretary
Welcoming Comments: Wiley A. Chambers, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

8:45 Open Public Hearing

Sponsor Presentation

Introduction: Michael S. Perry, DVM, PhD, Vice President
Drug Registration and Regulatory Affairs
Sandoz Pharmaceuticals Corporation

Clinical Efficacy and Safety

Dosing Guidelines: Helen Torley, MB, ChB, MRCP, Head
Medical Affairs, Sandoz Pharmaceuticals

Clinical Perspective: Peter Tugwell, MD, Chairman
Department of Medicine
University of Ottawa, Canada

10:45 **Break**

11:00 **FDA Presentation**

Medical: Kent R. Johnson, MD, Medical Officer
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, FDA

12:00 **Lunch**

1:00 **Discussion and Questions** #1 and #2

3:00 **Sponsor Presentation Pediatric Data:** Vibeke Strand, MD, FACP
Clinical Faculty, Stanford University, CA

3:30 **Discussion and Question #3**

5:00 **Adjourn**

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ISSUES TO CONSIDER

1. Has Neoral demonstrated efficacy in controlled trials and does it have an acceptable risk/benefit ratio?

2. How should its indication section read?

   In which "set of RA patients?

   In combination with background therapy (i.e. methotrexate)?

   a. Should separate recommendations (dosing, monitoring, etc.) be recommended in the presence of background methotrexate?

   b. Is there a significant PK interaction with Neoral and methotrexate?

      Is it clinically significant?

      If so, what are its implications regarding labeling?

3. What additional data, if any, would be needed in JRA to permit the labeling (via the "pediatric rule") for polyarticular JRA.

ARTHRITIS ADVISORY COMMITTEE
CENTER FOR DRUG EVALUATION AND RESEARCH

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Consultants to

Arthritis Advisory Committee
Food and Drug Administration
Center for Drug Evaluation and Research

February 4, 1997
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620 Perry Parkway, Gaithersburg, MD.

for **NDA 50-735, Neoral®, (cyclosporine) Sandoz**

VOTING:

Joseph McGuire, Jr., M.D.
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Stanford University School of Medicine
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M. Clinton Miller III, Ph.D.
Retired Professor and Chairman
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The George Washington University Medical Center
Associate Professor of Medicine and Child Health Development
Childrens National Medical Center
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HB Burns Building, Room 5-403
Washington, DC 20037

Agenda
Arthritis Advisory Committee
Food and Drug Administration
Center for Drug Evaluation and Research
Gaithersburg Hilton
620 Perry Parkway, Gaithersburg, MD
February 5, 1997

"Guidance for Industry. Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA)"

Open Session

8:00 a.m.	Call to Order, Introductions: Michelle Petri, Chair Meeting Statement: Kathleen Reedy, Executive Secretary	
8:15 a.m.	Open Public Hearing	
8:45 a.m.	Introduction to Document and Discussion of RA Claims Structure: Janet Woodcock	
	Signs & Symptoms	Janet Woodcock
	Pro/Con Debate re dropouts	Kent Johnson & Jeff Siegel
	Function/Quality of Life	Kent Johnson
	Structure (x-ray/other)	Jeff Siegel
10:30 a.m.	BREAK	
10:45 a.m.	Major Clinical Response	Kent Johnson
	"Toward a Data-Driven Definition"	David Felson
	Complete Clinical Response & Remission	William Schwieterman
12:00 noon	LUNCH BREAK	
1:15 p.m.	Preclinical and Early Clinical	Michelle Petri
1:35 p.m.	Equivalency Trials	Wiley Chambers
2:00 p.m.	Safety Analysis & Phase IV	Frederick Miller & William Schwieterman
3:00 p.m.	BREAK	
3:15 p.m.	Overview of JRA and subsets	Patience White

3:30 p.m. Application of Pediatric Rule, JRA Claims Structure, JRA Claims, and JRA Drug Development Lisa Rider

4:15 p.m Conclusions & Summary - Janet Woodcock, Michelle Petri

5:00 p.m. ADJOURN

Since this is not a discussion of a particular drug and we are requesting interaction and input from the Arthritis Advisory Committee members we have chosen to seat the table alphabetically (with Drs. Petri and Woodcock in the center) rather than the usual format.

After each short presentation, there will be discussion, questions & answers from the panel then it will be open to the audience for comments, questions & answers.

Consultants to

Arthritis Advisory Committee
Food and Drug Administration
Center for Drug Evaluation and Research

February 5, 1997
Gaithersburg Hilton
620 Perry Parkway, Gaithersburg, MD.

for DRAFT **GUIDANCE FOR INDUSTRY: CLINICAL DEVELOPMENT PROGRAMS FOR DRUGS, DEVICES AND BIOLOGICAL PRODUCTS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS (RA)**

Karyl S. Barron, M.D., Deputy Director
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Open Public Hearing

Arthritis Advisory Committee
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for DRAFT **GUIDANCE FOR INDUSTRY: CLINICAL DEVELOPMENT PROGRAMS FOR DRUGS, DEVICES AND BIOLOGICAL PRODUCTS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS (RA)**

SmithKlineBeecham Pharmaceuticals:

Paula Goldberg, Associate Director
United States Regulatory Affairs

Ken Seamon, Ph.D., Senior Vice President
Scientific Development

IDEC Pharmaceuticals:

Alan Solinger, M.D., Director
Clinical Therapeutics

Arthritis Advisory Committee

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Center for Drug Evaluation and Research

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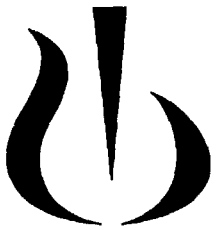
NDA 50-735, Neoral®, (cyclosporine) Sandoz

Contents

INTRODUCTION



NOVARTIS

Pharmaceuticals Corporation

Neoral® (cyclosporine for microemulsion)

Rheumatoid Arthritis

Michael S. Perry, DVM, PhD
Vice President, Drug Regulatory Affairs

NEORAL®
(cyclosporine for microemulsion)

- Severe, active rheumatoid arthritis (RA)
- NDA No. 50-735 (Soft Gelatin Capsules)
- NDA No. 50-736 (Oral Solution)

NEORAL RA—INDICATION

Neoral is indicated for the treatment of patients with severe, active rheumatoid arthritis (RA) in whom at least one slow-acting second-line drug is ineffective or not tolerated.

Neoral can be used in combination with methotrexate in RA patients who do not respond adequately to MTX alone.

CYCLOSPORINE—RATIONALE IN RA

- Cyclosporine (CsA) is an immunosuppressive drug.
- In the chronic joint inflammation that characterizes RA, macrophages and T cells are activated, releasing cytokines.
- CsA is thought to act largely by inhibiting the secretion of such cytokines (particularly interleukin-2) from T cells.

CsA REGULATORY HISTORY

- The original formulation of CsA, Sandimmune® (SIM), has been approved for prophylaxis of organ rejection in the United States since 1983.
- A microemulsion formulation of CsA, Neoral®, has been approved for prophylaxis of organ rejection in the United States since 1995.
- CsA has been approved for use in the treatment of severe RA, with more than 20,000 patients treated.
- Neoral has been approved for the treatment of severe RA in more than 70 countries.

NEORAL VS SIM

- Same active ingredient—CsA.
- Neoral is a microemulsion formulation of CsA.
- Neoral is more bioavailable than SIM.
- Some patients absorb SIM poorly.
- Most patients absorb Neoral well.
- Exposure to CsA is more consistent from patient to patient with Neoral than with SIM.
- Despite differences in pharmacokinetics, safety and efficacy are comparable with Neoral and SIM.

PRESENTATIONS

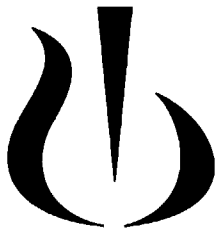
- Neoral is effective in the recommended dose range of 2.5-4.0 mg/kg/day.
- Combination therapy with MTX in patients responding inadequately to MTX alone provides additional benefit.
- Known side effects of CsA—renal, hypertension, immunosuppression, and others—can be managed when Neoral is used as recommended in labeling.

AGENDA

Introduction	Michael S. Perry, DVM, PhD
Efficacy	Helen Torley, MB, ChB, MRCP
Safety	
Dosing/Usage Guidelines	
Clinical Perspective	Peter Tugwell, MD
Pediatric Data	Vibeke Strand, MD

CONSULTANTS

EFFICACY



NOVARTIS

Pharmaceuticals Corporation

Helen Torley, MB, ChB, MRCP

Head, Medical Affairs

EFFICACY OF CsA/NEORAL IN RA PATIENTS

- Study populations
- Mechanism of action
- Study designs
- Patient characteristics
- CsA/Neoral results

OVERVIEW OF RA STUDIES IN THE 1980s

Initial CsA Dosage	Study	Study Design
≥10 mg/kg/day	**102**	open label
	104	pilot vs azathioprine
	106	vs placebo
≥5 mg/kg/day	**103**	open label
	105	open label
	107	open label
	5504	vs placebo
	2004	vs placebo
	2003	pilot vs azathioprine
	2002	vs D-penicillamine
	2005	vs azathioprine
	201	pilot (USA)
	202	pilot (USA)
	602	pilot (USA); NSAID interaction
4 mg/kg/day	**601**	pilot (USA)

OVERVIEW OF RA STUDIES IN THE 1990s

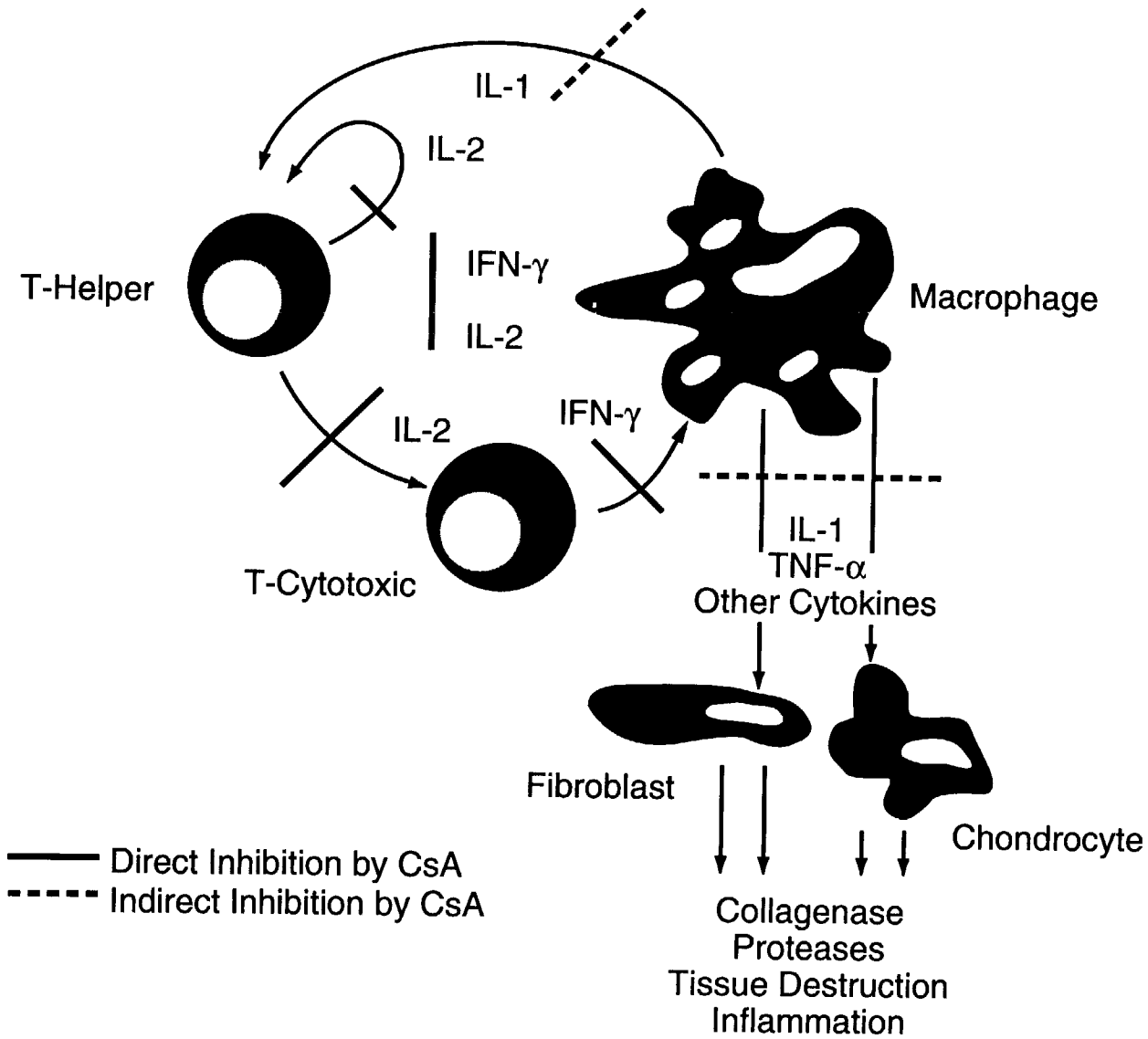
Initial CsA Dosage (mg/kg/day)	Study	Study Design	Duration	Extension
2.5	**2008**	blinded	6 mo	none
2.5	**651**	blinded	6 mo	up to 18 mo*
1.5, 2.5	**652**	blinded	4 mo	up to 20 mo*
1.5, 2.5, 4.0	**653**	blinded	3.5 mo	up to 12 mo
2.5	**302**	blinded	6 mo	6 mo
2.5	**654**	blinded	6 mo	12-18 mo
3.0	**2401**	single blind	18 mo	none
3.0	**2404**	open label	18 mo	18 mo
3.0	**I/002/91**	open label	12 mo	12 mo
Conversion	**301**	blinded	3 mo	9 mo
	303	open label	3 mo	9 mo

*Maximum of 2 yr.

POPULATIONS STUDIED/PRESENTED

- Labeling studies
  - Studies whose results are proposed to be presented in the Neoral label: 651, 652, and 2008; 302 (Neoral vs SIM); 654 (SIM + MTX vs placebo + MTX)
- CORE studies
  - Placebo-controlled SIM studies considered "pivotal": 651, 652, 653, and 2008
- Combined studies and 3 mg/kg/day open-label studies
  - Combined study experience with SIM
  - Presented predominantly in safety section

CsA MECHANISM OF ACTION



STUDY DESIGNS: DOUBLE-BLIND, RANDOMIZED PLACEBO-CONTROLLED STUDIES

	Study 651	Study 652	Study 653*	Study 2008
Treatment summary	SIM vs MTX vs placebo	SIM vs placebo	SIM vs placebo	SIM vs placebo
Country (no. of centers)	USA (14)	USA (16)	USA (9)	Canada (6)
Duration of treatment†	24 wk	16 wk	14 wk	24 wk
Type of patient	Active RA; failed ≥1 SAARD	Active RA; failed ≥1 SAARD	Active RA; failed ≥1 SAARD	Active RA; previously unresponsive to conventional treatment
Treatment group (n)‡				
SIM 1.5 mg/kg/day§	–	90	48	–
SIM 2.5 mg/kg/day§	101	97	47	72
SIM 4.0 mg/kg/day§	–	–	49	–
MTX ≤15 mg/wk§	96	–	–	–
Placebo	67	63	50	72
Total no. of patients	264	250	194	144

*Dosage adjustments were made to maintain target trough levels, not for clinical response.
†Extension studies not included.
‡Randomized population.
§Initial dosage.

STUDY 302
Double-Blind Randomized Study

Treatment summary	Neoral vs SIM
Country (no. of centers)	USA and Europe (37)
Duration of treatment	24 wk (+ 28-wk double-blind extension)
Type of patient	Severe, active RA, in whom treatment with SAARD(s) is ineffective or inappropriate
Treatment group (n)*	
Neoral 2.5 mg/kg/day†	144
SIM 2.5 mg/kg/day†	155
Total no. of patients	299

*Randomized population.
†Initial dosage.

STUDY 654
Double-Blind Randomized Study

Treatment summary	SIM + MTX vs placebo + MTX
Country (no. of centers)	USA and Canada (5)
Duration of treatment*	24 wk
Type of patient	Active RA; inadequate response to MTX
Treatment group (n)†	
SIM 2.5 mg/kg/day‡ + MTX ≤15 mg/wk	75
MTX ≤15 mg/wk + placebo	73
Total no. of patients	148

*Extension studies not included.
†Randomized population.
‡Initial dosage.

PATIENT DEMOGRAPHICS
Placebo-Controlled Studies

	Study 651			Study 652		Study 653		Study 2008	
Treatment group	SIM	MTX	placebo	SIM	placebo	SIM	placebo	SIM	placebo
No. of patients randomized	101	96	67	187	63	144	50	72	72
Age (mean, yr)	48.7	52.1	50.6	53.1	50.0	50.9	50.7	54.6	55.0
Gender (% females)	75	75	79	79	79	76	82	68	74
RA duration (mean, yr)	10.6	10.4	9.0	12.9	12.8	12.1	11.9	10.7	11.2
Concomitant NSAIDs (%)	92	95	96	82	92	93	90	71	67
Concomitant steroids (%)	63	67	81	82	86	89	86	61	63

PATIENT DEMOGRAPHICS
Study 302

Treatment group	Neoral 2.5 mg/kg/day*	SIM 2.5 mg/kg/day*
No. of patients randomized	144	155
Age (mean, yr)	53.4	54.0
Gender (% females)	76	78
RA duration (mean, yr)	11.1	10.9
No. of prior SAARDs (mean)	3.4	3.4
Concomitant NSAIDs (%)	74	77
Concomitant steroids (%)	72	72

*Initial dosage.

PATIENT DEMOGRAPHICS
Study 654

Treatment group	SIM + MTX	Placebo + MTX
No. of patients randomized	75	73
Age (mean, yr)	56.4	54.6
Gender (% females)	75	72
RA duration (mean, yr)	11.2	9.4
No. of prior SAARDs (mean)	2.4	2.2
Concomitant NSAIDs (%)	87	92
Concomitant steroids (%)	69	74

MEAN SJC AND TJC AT BASELINE
Studies 651, 652, 2008, 302, and 654

Studies	Treatment Group	SJC	TJC
651	SIM	19.4	24.1
	MTX	17.8	24.1
	Placebo	17.0	23.1
652	SIM 1.5 mg/kg/day*	20.7	21.4
	SIM 2.5 mg/kg/day*	20.0	21.0
	Placebo	19.1	15.4
2008	SIM	14.63	35.27
	Placebo	14.35	33.33
302	Neoral	17.83	23.29
	SIM	16.80	24.56
654	SIM + MTX	16.0	19.1
	Placebo + MTX	17.3	20.6

* Initial dosage.

DOSE TITRATION
Labeling Studies

- Initial patient dosages were randomized
- Study 2008
  - Initial goal was to reach target trough level; however, because blood levels were too inconsistent, actual adjustments were made to increase dosage until serum creatinine rose
- Studies 651 and 652
  - Increased dosage by increments of 50 or 100 mg after 8 weeks, not exceeding 5 mg/kg/day
- Study 302
  - Increased dosage after 4 weeks to the following dosages
    - 3.3, 4.2, 5.0 mg/kg/day, not exceeding 5 mg/kg/day
- Study 654
  - Increased dosage by 0.5 mg/kg/day at weeks 2, 4, 8, and 16, unless signs of toxicity were seen, not exceeding 5 mg/kg/day

DOSAGE OF CsA BY LABELING STUDY

Study		CsA Dosage (mg/kg/day) Initial	Range of Actual Dosages	Mean at Final Study Week
651	SIM	2.5	0.8-5.3	3.1
652	SIM	1.5	0.9-5.7	2.4
	SIM	2.5	0.9-5.1	2.9
2008	SIM	2.5	0.2-9.26	3.6
302	Neoral	2.5	0.72-5.26	2.9
	SIM	2.5	0.38-5.68	3.3
654	SIM + MTX	2.5	0.3-4.1	2.8

PATIENT DISCONTINUATIONS*
Placebo-Controlled Studies

	Study 651			Study 652			Study 653				Study 2008	
	SIM 2.5†	MTX	Placebo	SIM 1.5†	SIM 2.5†	Placebo	SIM 1.5†	SIM 2.5†	SIM 4.0†	Placebo	SIM 2.5†	Placebo
Percent of patients completing	**57**	69	36	82	**77**	71	73	**72**	86	58	**86**	69
Reasons for discontinuations												
Lack of efficacy (%)	**21**	8	52	9	**5**	10	13	**6**	2	32	**4**	29
Adverse event (%)	**9**	14	5	6	**7**	6	2	**13**	12	0	**6**	1
Other (%)	**13**	9	7	3	**10**	13	13	**9**	0	10	**4**	0

*Values reported are for the randomized population.
†Initial dosage (mg/kg/day).

PATIENT DISCONTINUATIONS*
Studies 302 and 654

	Study 302		Study 654	
	Neoral	SIM	SIM + MTX	Placebo + MTX
Percent of patients completing	68	63	76	84
Reasons for discontinuations				
Lack of efficacy (%)	6	8	1	4
Adverse event (%)	13	21	9	7
Other (%)	13	8	13	5

*Values reported are for the randomized population.

EFFICACY RESULTS

- Primary efficacy variables as stated in individual protocols
- ACR Responder Index (only patients completing the study can be responders)

MEAN CHANGES IN PRIMARY EFFICACY CRITERIA IN STUDY 651*

Change From Baseline at End Point

	SIM 2.5 mg/kg/day**	MTX	Placebo
SJC	**-2.7†**	-4.4†	1.8
TJC	-2.6	-8.4†	1.7
Pt global‡	**3.3†**	2.4†	3.8
MD global‡	**3.2†**	2.5†	3.9
HAQ	**-0.1†**	-0.2†	0.1

*Values reported are for the ITT population.
**Initial dosage.
†$P<0.05$, treatment vs placebo.
‡Mean at end point.

MEAN CHANGES IN PRIMARY EFFICACY CRITERIA IN STUDY 652*

Change From Baseline at End Point

	SIM 1.5 mg/kg/day**	SIM 2.5 mg/kg/day**	Placebo
SJC	-1.9	**-5.5†**	-1.8
TJC	-0.8	**-5.8†**	-0.4
Pt global‡	3.4	**3.2†**	3.8
MD global‡	3.6	**3.2†**	3.9
HAQ	0.1	**-0.1†**	0.2

*Values reported are for the ITT population.
**Initial dosage.
†$P<0.05$ SIM vs placebo.
‡Mean at end point.

MEAN CHANGES IN PRIMARY EFFICACY CRITERIA IN STUDY 653*

Change From Baseline at End Point

	SIM 1.5 mg/kg/day**	SIM 2.5 mg/kg/day**	SIM 4.0 mg/kg/day**	Placebo
SJC	-2.4	-6.3	-5.1	-3.5
TJC	-2.6	-6.2	-7.1	-3.7
Pt global	-0.4	**-0.9†**	**-1.0†**	-0.3
MD global	-0.4	**-0.9†**	**-1.0†**	-0.3
HAQ	0.0	-0.1	-0.2	0.0

*Values reported are for the ITT population.
**Initial dosage.
† $P<0.05$, SIM vs placebo.

MEAN CHANGES IN SELECTED EFFICACY CRITERIA IN STUDY 2008*

Change From Baseline at End Point

	SIM 2.5 mg/kg/day**	Placebo
SJC	**-3.2†**	0.2
TJC	**-9.2†**	0.3
Pt global‡	**2.1†**	3.4
MD global‡	**2.1†**	3.4
VAS pain	**-2.2†**	-0.3

*Values reported are for the ITT population.
**Initial dosage.
†$P<0.05$, SIM vs placebo.
‡Mean at end point.

MEAN CHANGES IN SELECTED EFFICACY CRITERIA IN STUDY 302*

Change From Baseline at End Point

	Neoral 2.5 mg/kg/day**	SIM 2.5 mg/kg/day**
SJC	-5.0	-4.4
TJC	-8.4	-6.5
Pt global	**-0.9†**	-0.6
MD global	-0.8	-0.7
HAQ	-0.3	-0.2

*Values reported are for the ITT population.
**Initial dosage.
† $P<0.05$, Neoral vs SIM.

MEAN CHANGES IN PRIMARY EFFICACY CRITERIA IN STUDY 654*

Change From Baseline at End Point

	SIM + MTX	Placebo + MTX
SJC	**-6.3†**	-2.2
TJC	**-8.1†**	-3.0
Pt global	**-0.7†**	-0.1
MD global	**-0.8†**	-0.2
HAQ	**-0.26†**	-0.03

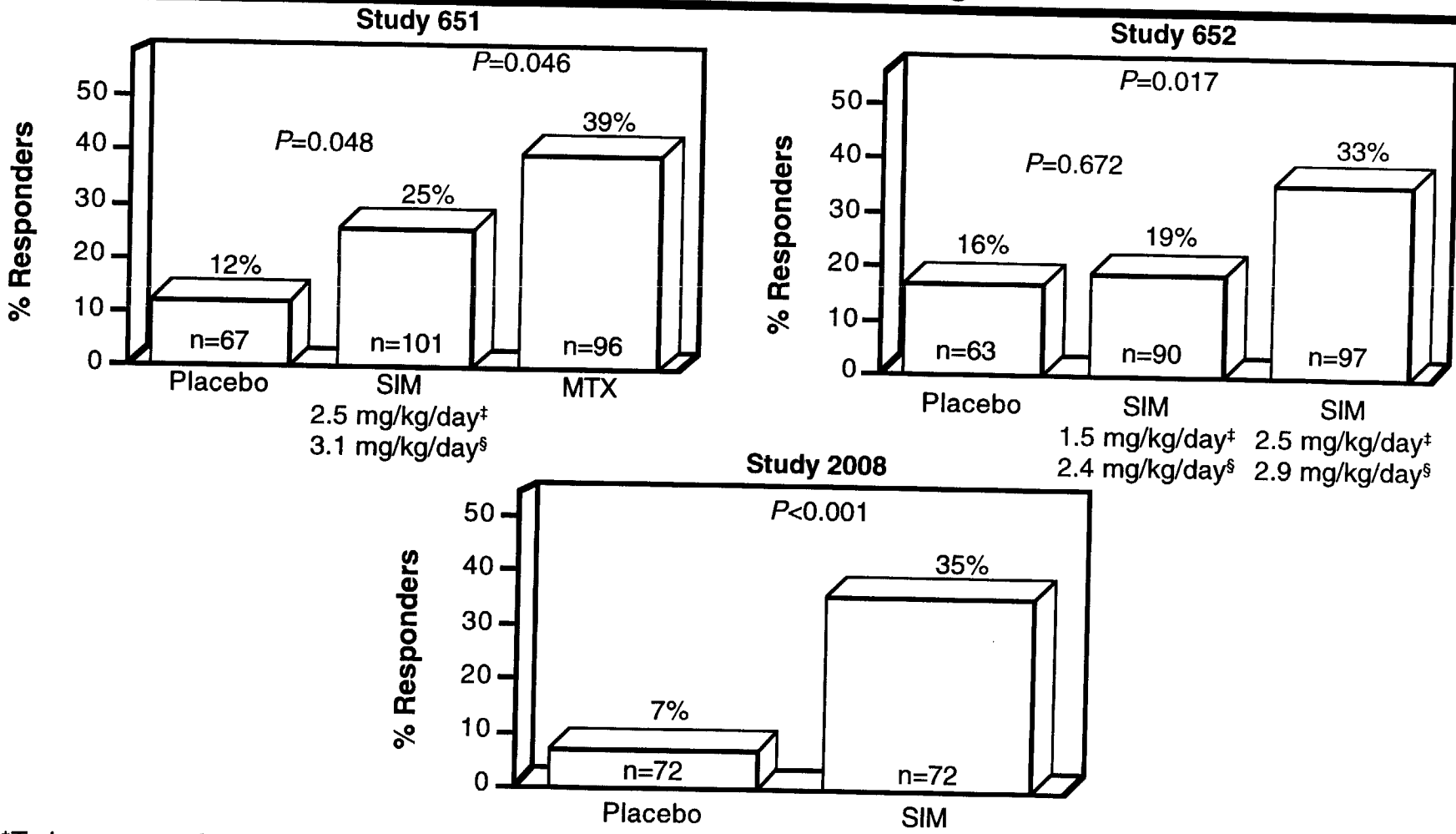
*Values reported are for the ITT population.
†$P<0.05$, SIM + MTX vs placebo + MTX.

WHO/ILAR/ACR CRITERIA* BY STUDY

Study	SJC	TJC	Pt Global	MD Global	ESR	HAQ	VAS Pain
651	✓	✓	✓	✓	✓	✓	–
652	✓	✓	✓	✓	✓	✓	–
2008	✓	✓	✓	✓	✓	–	✓
302	✓	✓	✓	✓	✓	✓	✓
654	✓	✓	✓	✓	✓	✓	✓

*Criteria for response: ≥20% improvement in SJC and TJC as well as ≥20% improvement in three of the remaining five parameters.

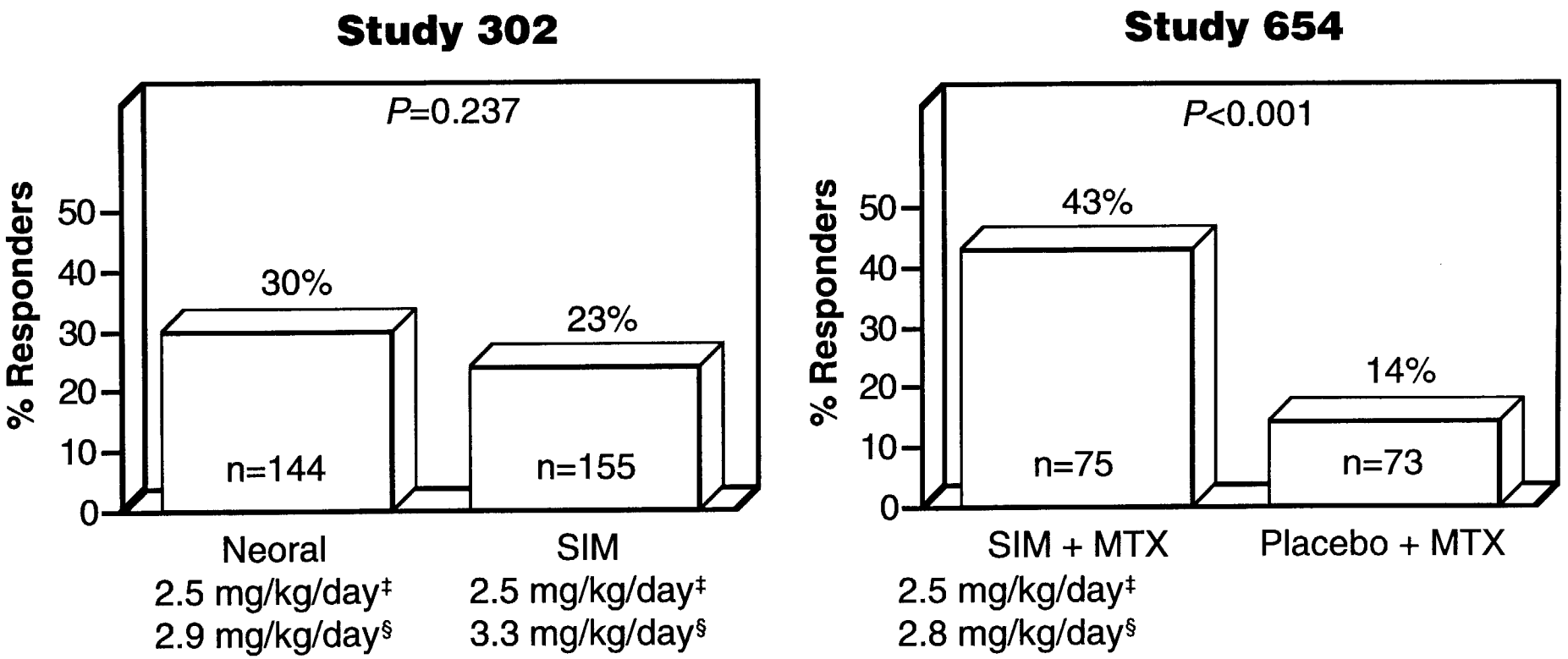
PERCENT RESPONDERS ACCORDING TO ACR CRITERIA* VS DOSAGE†
Placebo-Controlled Labeling Studies



*To be a responder, patient must also have completed the study.
†Values reported are for the randomized population.
‡Initial dosage.
§Mean dosage at last protocol visit.

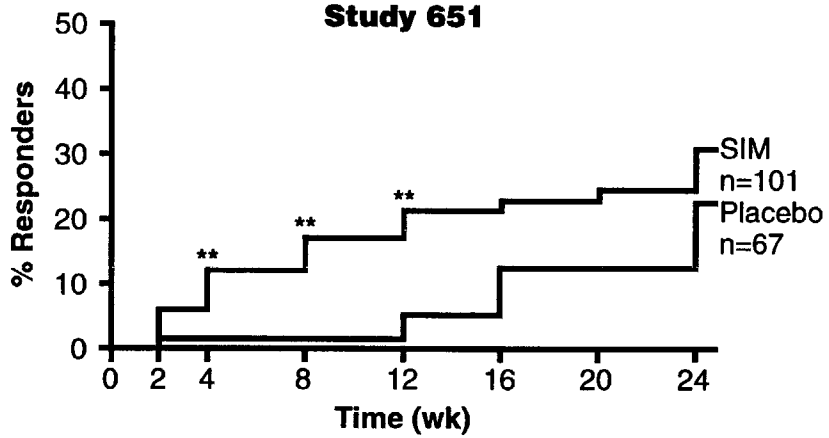
PERCENT RESPONDERS ACCORDING TO ACR CRITERIA*†

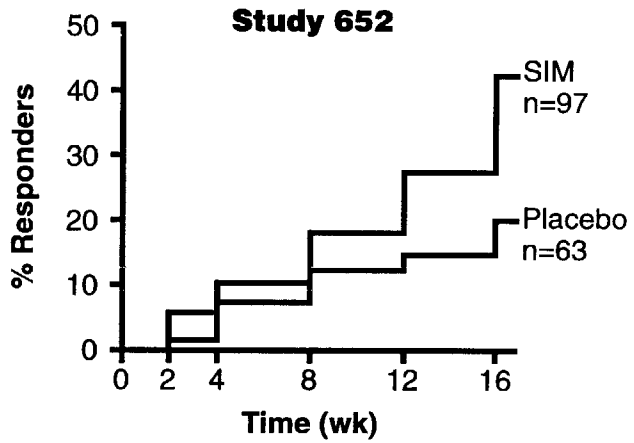
Studies 302 and 654

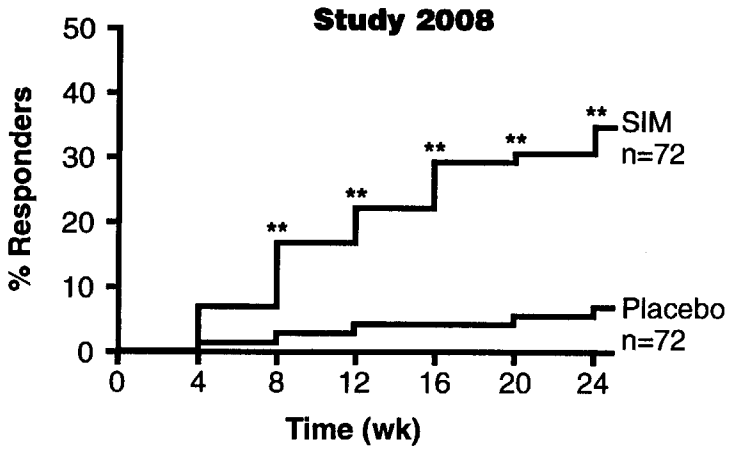


*To be a responder, patient must also have completed the study.
†Values reported are for the randomized population.
‡Initial dosage.
§Mean dosage at last protocol visit.

TIME TO ONSET OF RESPONSE*†
Cumulative Rate—SIM (2.5 mg/kg/day) vs Placebo





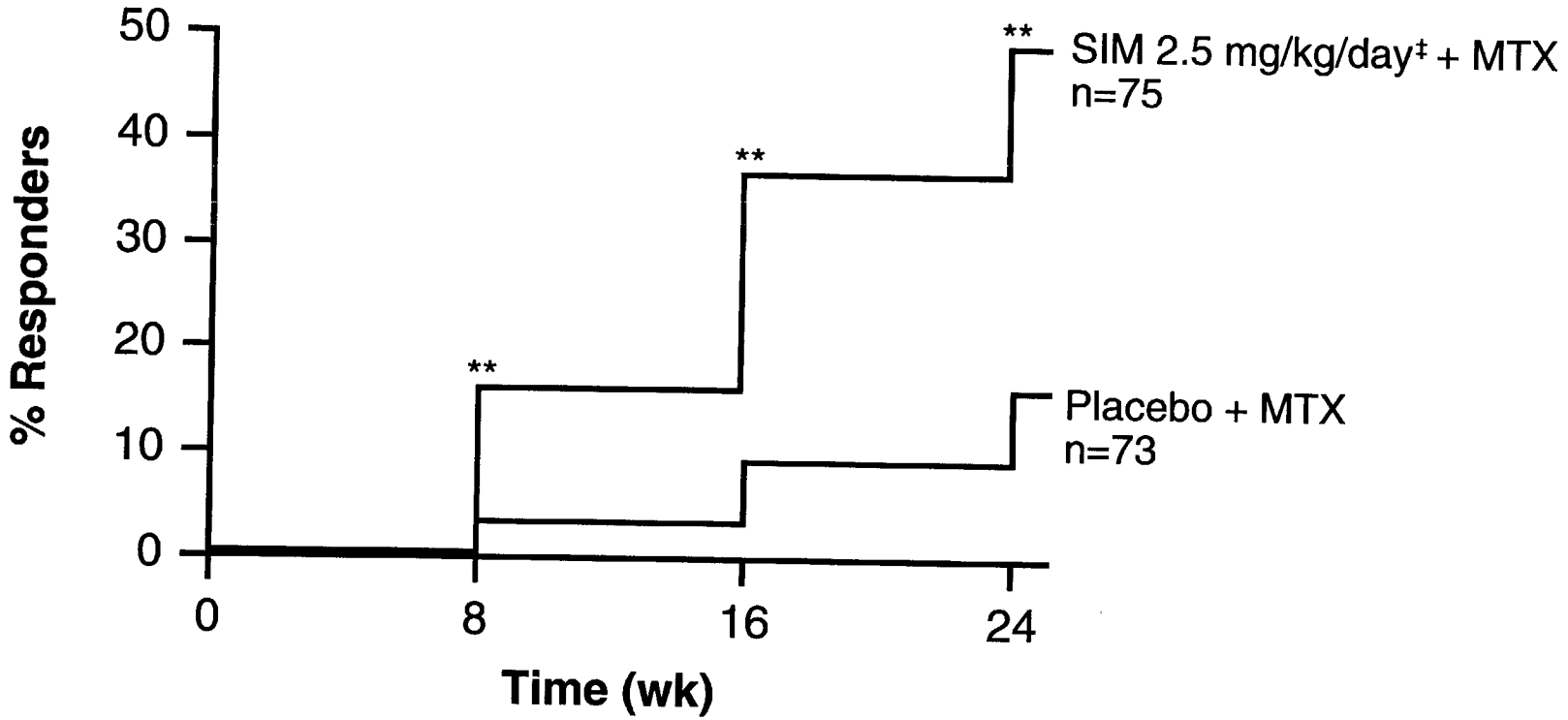


*First time to achieve 20% improvement in SJC and TJC plus 20% improvement in two or more of four additional efficacy variables. To be a responder, patient must also have completed the study.

**$P<0.05$, SIM vs placebo.

†Values reported are for the randomized population.

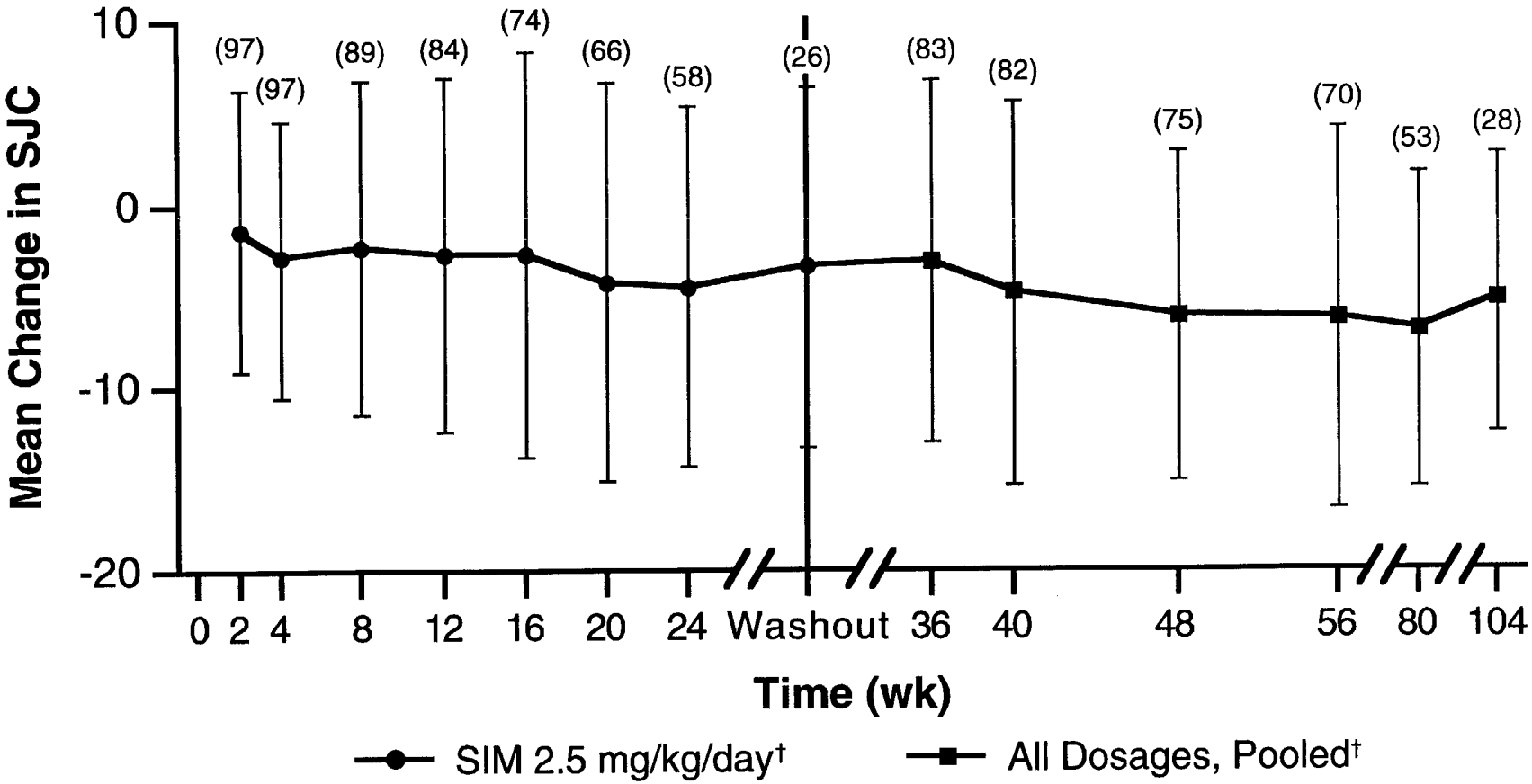
TIME TO ONSET OF RESPONSE*†
Cumulative Rate—Study 654



*Values reported are for the randomized population.
†First time to achieve 20% improvement in SJC and TJC plus 20% improvement in two or more of four additional efficacy variables. To be a responder, patient must also have completed the study.
** $P<0.05$, SIM + MTX vs placebo + MTX.
‡Initial dosage.

LONG-TERM EFFECT OF CsA TREATMENT

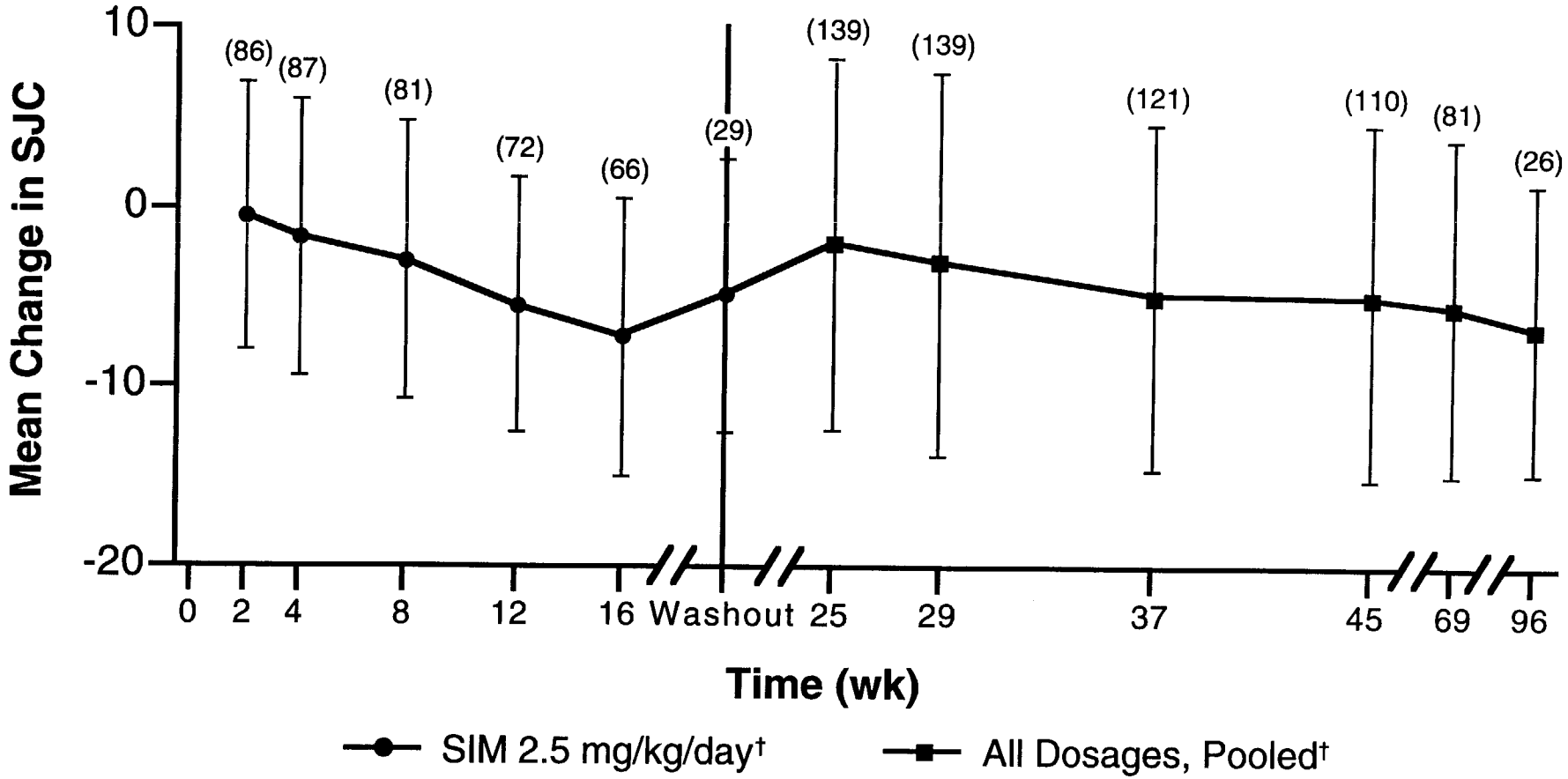
Change in SJC From Baseline—Study 651*



Mean, SD, (n).
*Values reported are for the ITT population.
†Initial dosage.

LONG-TERM EFFECT OF CsA TREATMENT

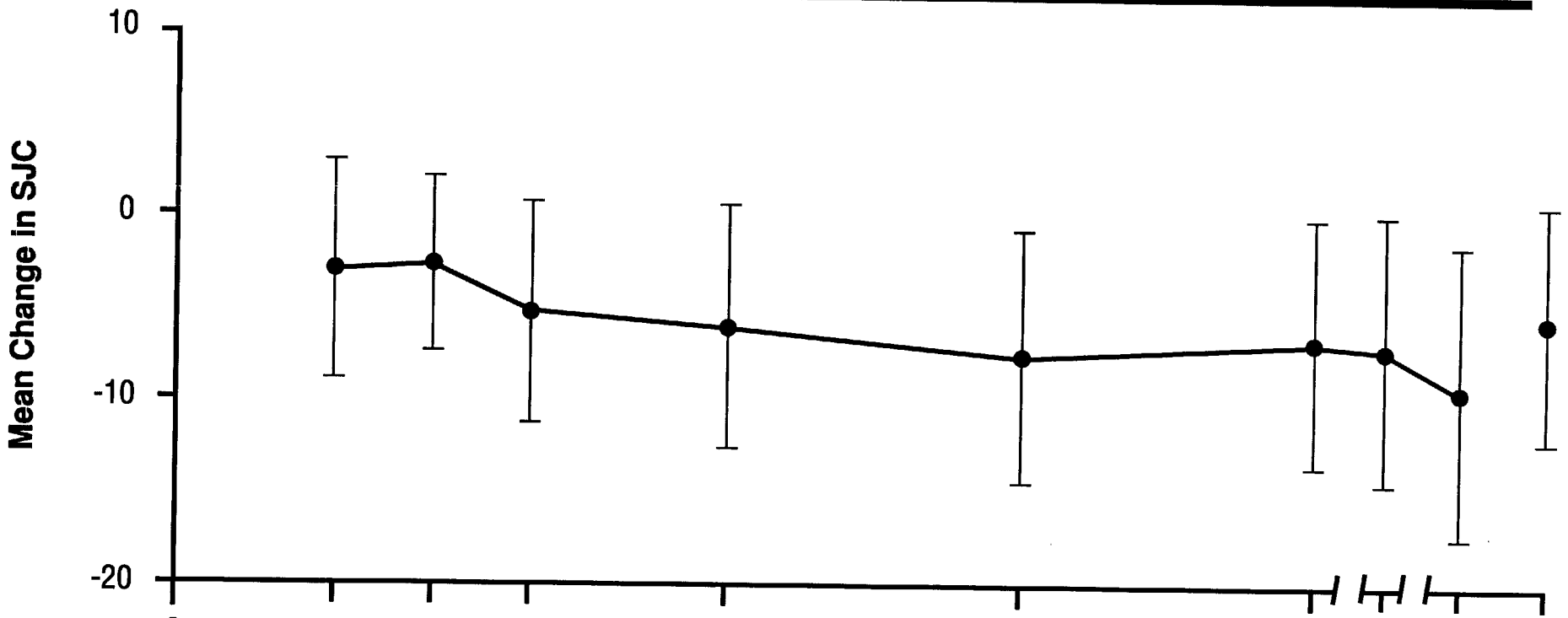
Change in SJC From Baseline—Study 652*



Mean, SD, (n).
*Values reported are for the ITT population.
†Initial dosage.

CHANGE IN SJC DURING CsA + MTX TREATMENT

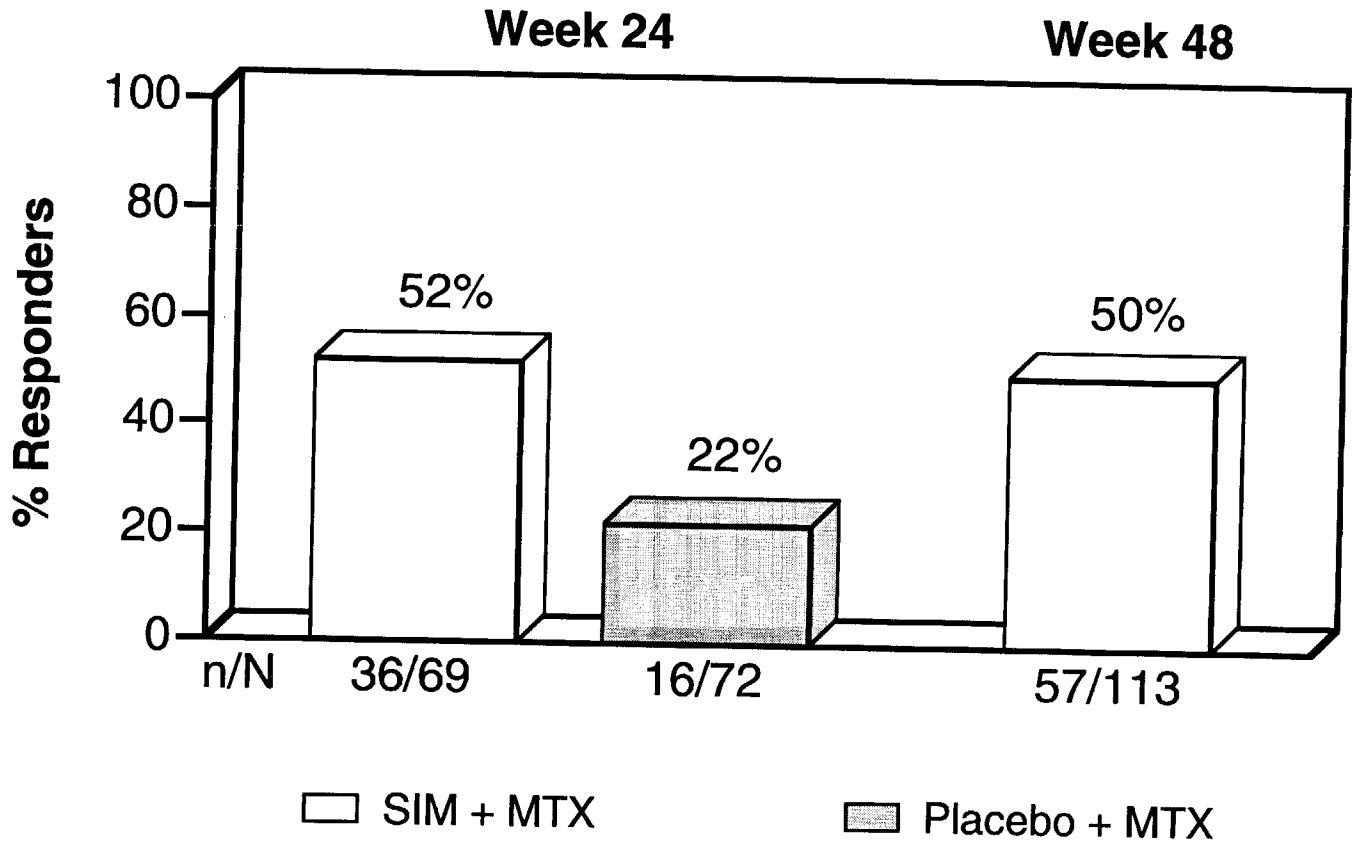
Study 654 (0 to 96 Weeks)*



No. of Patients	68	41	64	99	47	68	42	21	113
Mean SJC at Baseline	16.2	13.9	16.6	15.7	16.3	16.3	17.3	18.1	15.9

*Values reported are for the ITT population.

SUSTAINED EFFECT OF CsA
Percent ACR Responders*†—Study 654



*Values reported are for the ITT population.
†End point analysis.

EFFECT OF SIM DOSAGE TAPER AND WASHOUT ON TJC

Study	Taper (wk)	Washout (wk)	SIM Dosage (mg/kg/day)*	n†	Baseline Mean TJC	Mean Change From Baseline TJC	
						Final Week of Treatment	End of Washout
651	4	4	2.5	26	21.7	-5.8	-1.7
652	1	4	1.5	30	25.3	-6.3	-2.2
			2.5	29	22.0	-10.0	-4.1

*Initial dosage.

†Patients who completed washout period.

EFFICACY SUMMARY

- CsA (Neoral/SIM) produces statistically and clinically significant improvement in signs, symptoms, and function in RA disease activity
- Neoral produces comparable efficacy to SIM
- Onset of action occurs between 4 and 8 weeks
- An initial dosage of 2.5 mg/kg/day titrated for clinical response and safety is recommended
- The addition of CsA (Neoral/SIM) to the treatment of patients responding inadequately to MTX alone conferred a statistically significant clinical benefit

SAFETY

PATIENT POPULATIONS

		Patient CsA Exposure (n)					
	Studies	**>4 Mo**	**>8 Mo**	**>12 Mo**	**>18 Mo**	**>24 Mo**	**>30 Mo**
Placebo-controlled (N=502)	651, 652, 653, 2008, and extensions	403	254	163	72	32	3
Combined (N=1028)*	102, 103, 104, 105, 106, 107, 201, 202, 601, 602, 2002, 2003, 2004, 2005, 5504, 651, 652, 653, 2008, and extensions	825	440	274	143	40	16
Neoral vs SIM (Neoral, n=190; SIM, n=182)	301, 302, 303, and extensions	N=154; S=142	N=113; S=93	N=64; S=48	N=0; S=0	N=0; S=0	N=0; S=0
SIM + MTX vs Placebo + MTX (N=114)	654 and extension	99	59	58	47	24	0
	Subtotal	1220	705	444	190	64	16
Early RA (N=454)	2401, 2404, and I/002/91	—	—	156†	86†	70†	81†
	Total	—	—	600	276	134	97

*Exposure data not available for six patients in study 102.
†Does not include data from study I/002/91 since data are not available for the 12-month extension.

ADVERSE EVENT SUMMARY

- Adverse events occurring in significantly more SIM vs placebo patients
  - Gastrointestinal: nausea, dyspepsia
  - Central nervous system: headache, dizziness, paresthesia
  - Cardiovascular: hypertension, chest pain
  - Skin: hypertrichosis
  - Renal: serum creatinine increase
- Combination SIM + MTX resulted in a similar AE profile
  - Hypertrichosis and serum creatinine increase seen more commonly with SIM + MTX
- Neoral had a similar AE profile to SIM

ADVERSE EVENT DROPOUTS* BY BODY SYSTEM

Studies 651, 652, 653, and 2008†—Percentage of Patients

Body System/ Adverse Event	SIM‡ (n=317)	Placebo (n=252)	MTX (n=96)
Gastrointestinal	4	2	7
Laboratory abnormality	2	0	4
Central nervous system	1	<1	2
Body as a whole	<1	<1	1
Pulmonary	<1	<1	1
Skin	<1	<1	1
Infections	0	0	2
Vascular	1	0	1
Skeletal	<1	0	1
Endocrine	<1	0	0
Genitourinary	<1	0	0
Tumors	<1	0	0

*Values reported are for the randomized population.
†Extension studies not included.
‡2.5 mg/kg/day initial dosage.

SUMMARY OF DEATHS DURING OR FOLLOWING CLINICAL STUDY PARTICIPATION

	Neoral	SIM
Combined studies,* n/N (%)	—	12/1028 (1)
Early RA studies	—	4/454 (<1)
Studies 301, 302, and 303,* n/N (%)	1/190 (<1)	1/182 (<1)
Study 654,* n/N (%)	—	2/75 (3)
Causes		
Acute bacterial endocarditis	0	1
Aspergillosis	0	1†
Cardiovascular	0	4†
Cerebrovascular accident	0	1
Neoplasia	0	5‡
Pancreatitis/cholelithiasis	0	2†
Pulmonary fibrosis (preexisting)	0	1
Transfusion reaction, renal amyloid	0	1†
Sepsis	0	1
Trauma	0	1
Unknown§	1†	1†
Total	1	19

*Patients in extension studies included.
†One death occurred post–CsA treatment.
‡Two deaths occurred post–CsA treatment.
§Death unrelated to study participation.

CAUSES OF DEATH IN PLACEBO-CONTROLLED STUDIES*

Cause of Death	SIM† (n=608)	Placebo (n=358)
Brain carcinoma	1	0
Cerebrovascular accident	0	0
Pancreatitis	1	0
Pulmonary embolism	0	1
Sepsis	1	0
Transfusion reaction, renal amyloid	0	0
Thrombocytopenic purpura	0	1
Total	3	2

*Includes studies 651, 652, 653, 2008, 2004, 5504, and 106.
†Extension studies excluded.

SPECIAL SAFETY TOPICS

- Renal
- Hypertension
- Lymphoproliferative disorders

CsA RENAL EFFECTS

- Functional changes
- Morphological alterations

CsA-INDUCED ACUTE CHANGES IN RENAL FUNCTION

- Vasoconstriction of glomerular afferent arteriole

→ Reduction in renal blood flow

→ Reduction in glomerular filtration rate

→ Increase in serum creatinine

MAIN FEATURES OF CsA-ASSOCIATED NEPHROPATHY

- Tubulointerstitial changes
  - Focal interstitial fibrosis (striped) and tubular atrophy
- Arteriolar alterations
  - Intimal hyalinosis
  - CsA arteriolopathy

RISK FACTORS OF CsA NEPHROPATHY* IN AUTOIMMUNE DISEASE†

Patients (N=192) With Immune-Mediated Diseases Treated With SIM (3-20 mg/kg/day) for 4 to 39 Months

Variable	*P* Value
Maximum serum creatinine increase	0.0001
Maximum SIM dosage	0.0026
Age	0.0345
Duration of SIM treatment	>0.20
Duration of serum creatinine increase	>0.20
Hypertension	>0.20

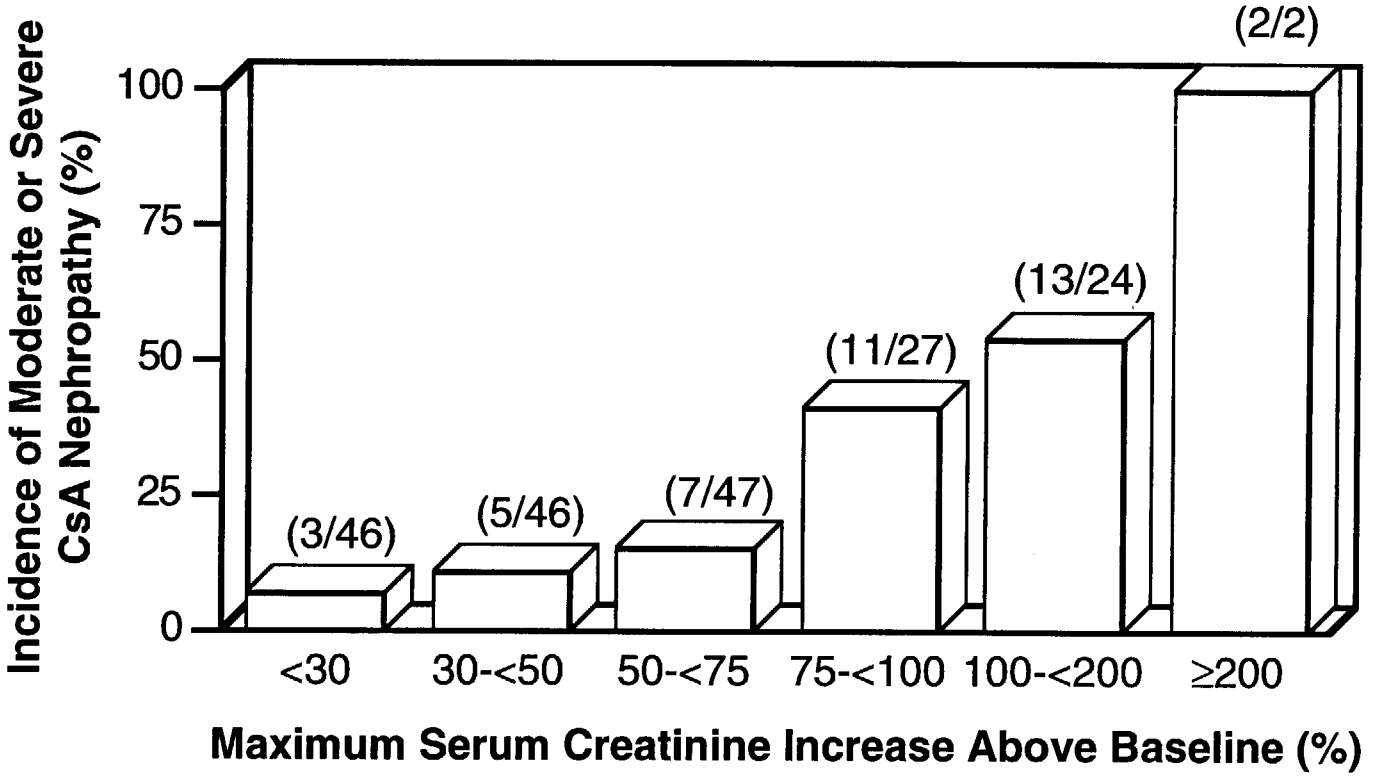
*At least moderate interstitial fibrosis or tubular atrophy, or typical arteriolopathy.

†International Kidney Biopsy Registry of SIM in Autoimmune Diseases.

Feutren G et al. *N Engl J Med.* 1992;326:1654.

RISK OF CsA NEPHROPATHY ACCORDING TO MAXIMUM SERUM CREATININE INCREASE*

Patients (N=192) With Immune-Mediated Diseases Treated With SIM (3-20 mg/kg/day) for 4 to 39 Months



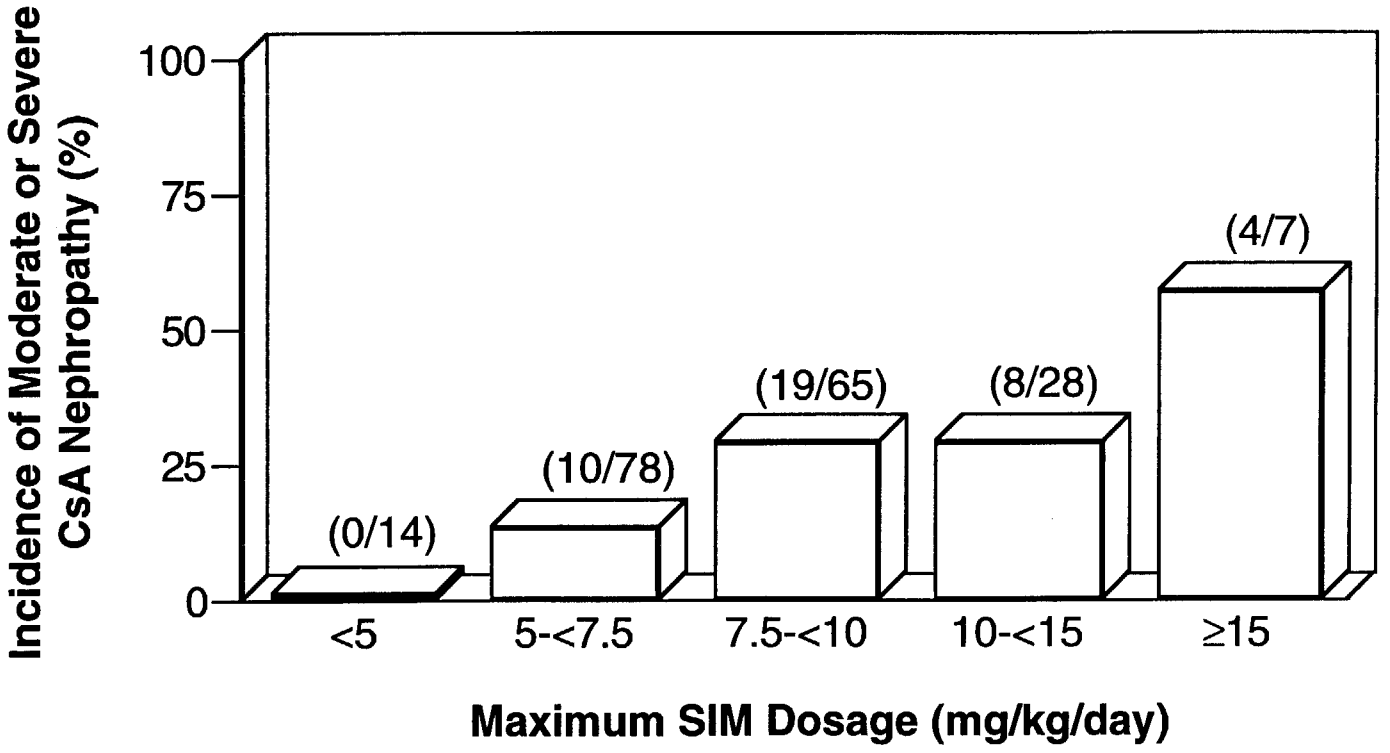
(n/N).

*International Kidney Biopsy Registry of SIM in Autoimmune Diseases.

Feutren G et al. *N Engl J Med.* 1992;326:1654.

RISK OF CsA NEPHROPATHY ACCORDING TO MAXIMUM CsA DOSAGE*

Patients (N=192) With Immune-Mediated Diseases Treated With SIM (3-20 mg/kg/day) for 4 to 39 Months



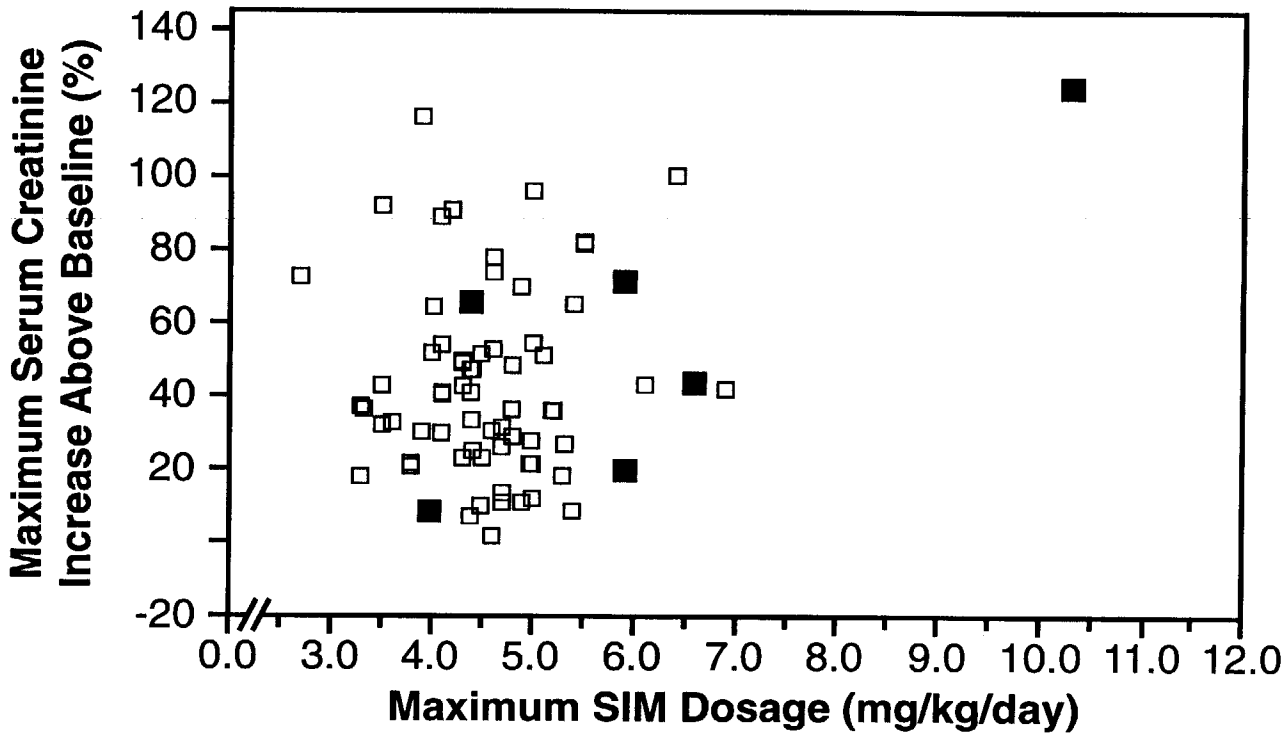
(n/N).

*International Kidney Biopsy Registry of SIM in Autoimmune Diseases.

Feutren G et al. *N Engl J Med.* 1992;326:1654.

KIDNEY BIOPSIES IN CsA-TREATED RA PATIENTS

Correlation Between Maximum SIM Dosage, Maximum Serum Creatinine Increase, and Nephropathy*



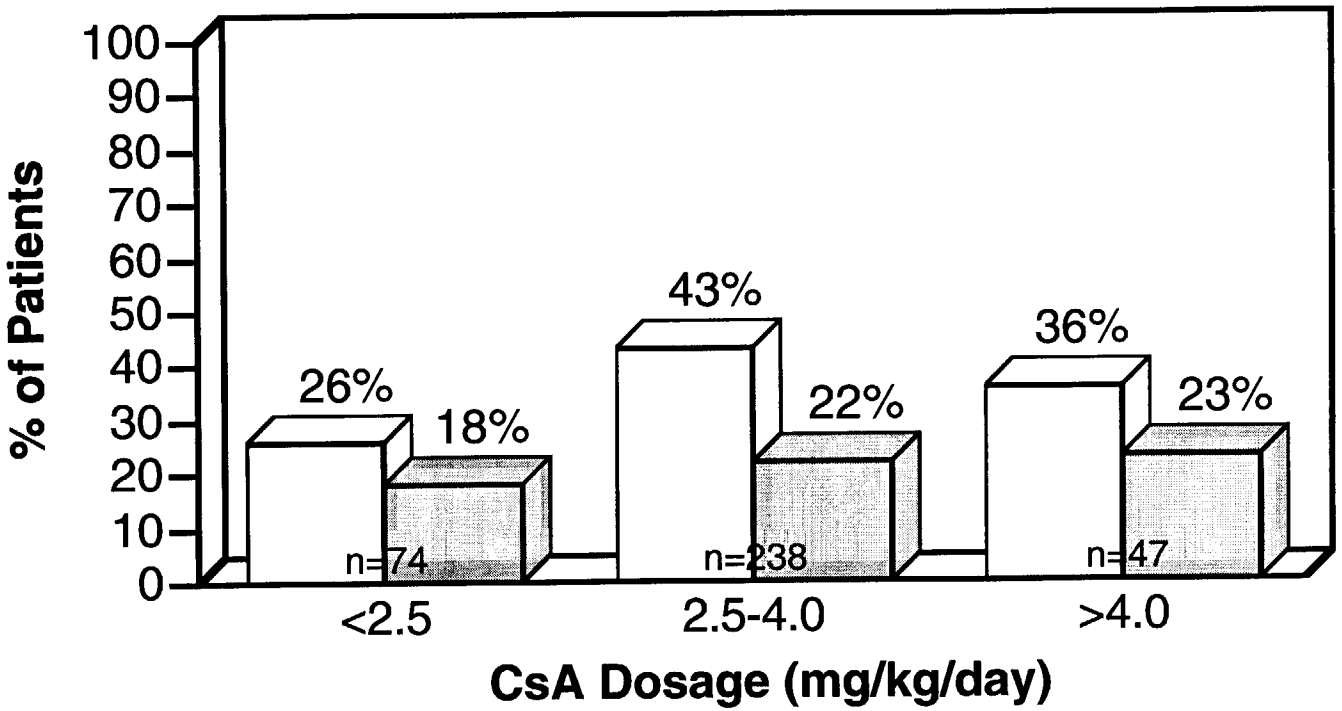
*Treatment characteristics from baseline until first biopsy reported.

†Five patients had nephropathy at first biopsy; one patient had nephropathy only on second biopsy.

Feutren G et al. *Br J Rheumatol.* 1993;32(suppl 1):65.
Rodriguez F et al. *Arthritis Rheum.* 1996;39:1491.

CUMULATIVE INCIDENCE OF SERUM CREATININE ELEVATION BY CsA DOSAGE* GROUP AT WEEK 24

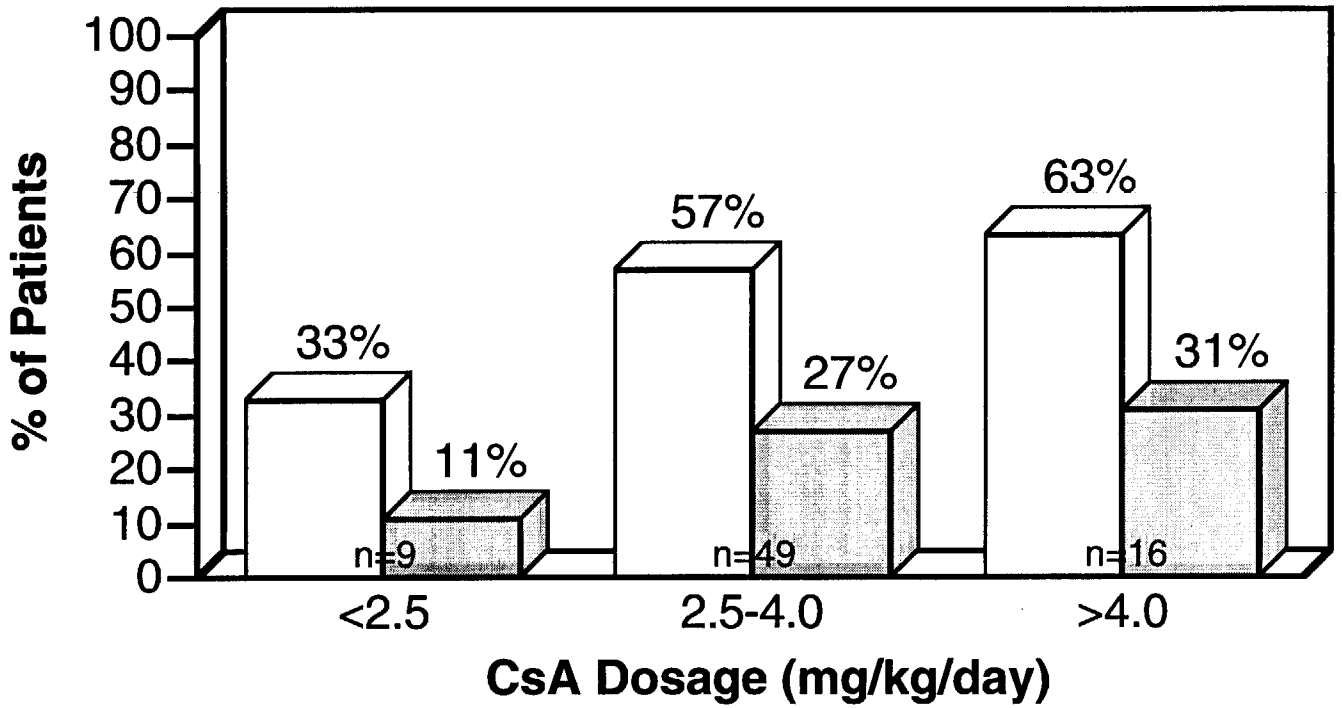
Studies 651, 652, and 2008—Percentage of Patients



*Maximum dosage.

CUMULATIVE INCIDENCE OF SERUM CREATININE ELEVATION BY CsA DOSAGE* GROUP

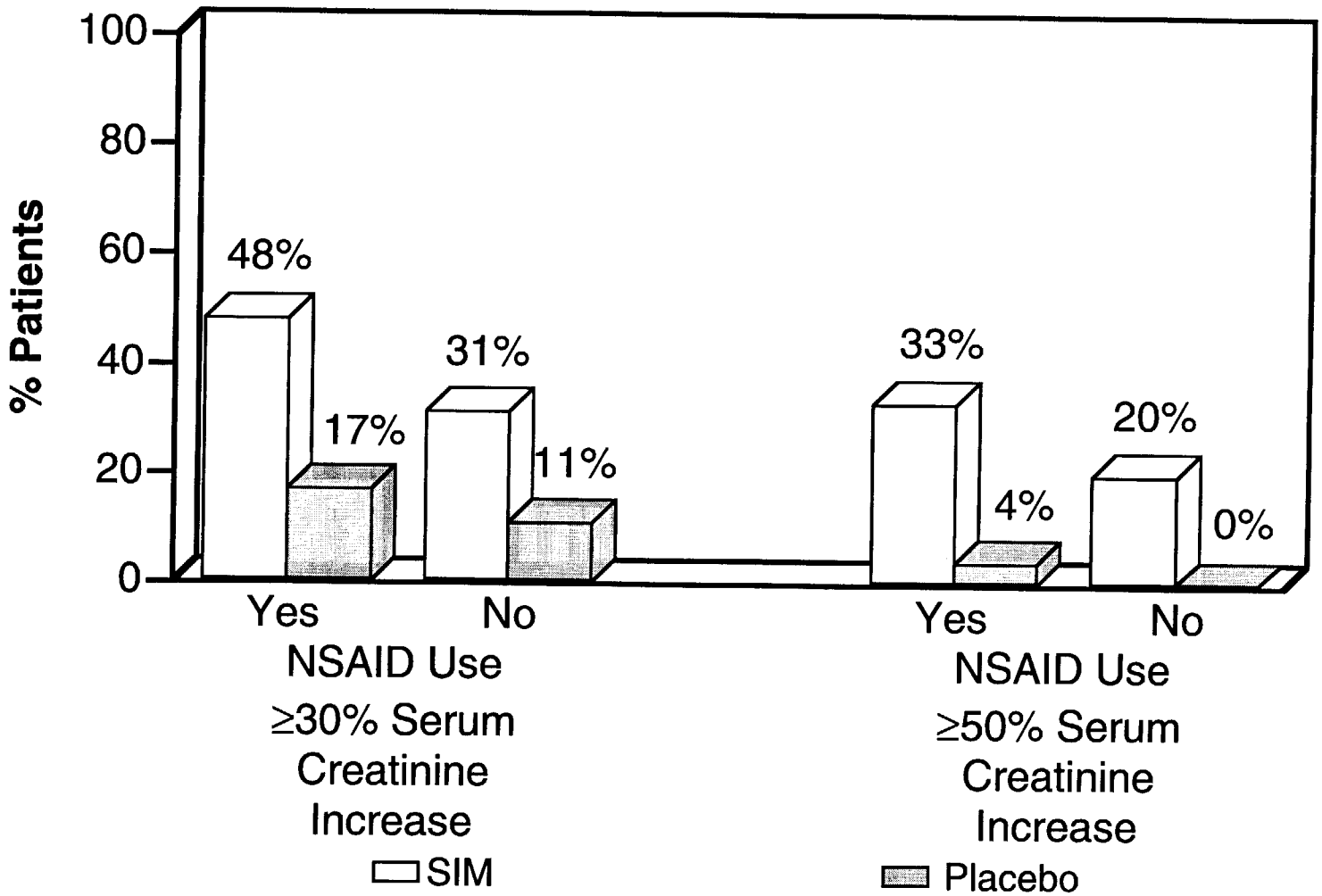
Study 654—Percentage of Patients



*Maximum dosage.

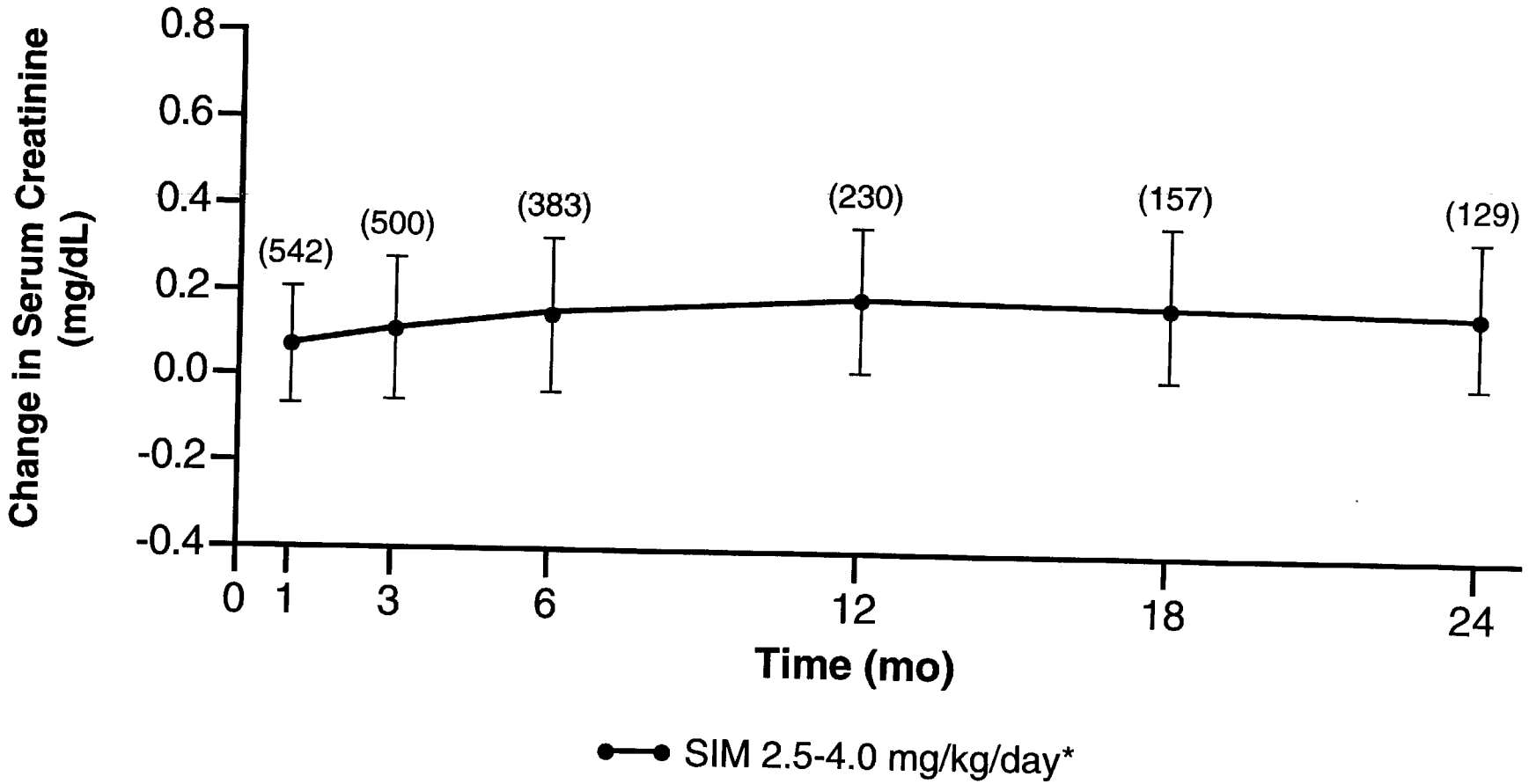
CUMULATIVE INCIDENCE OF ≥30% AND ≥50% INCREASE IN SERUM CREATININE BY NSAID USE

Studies 651, 652, and 2008—2.5 mg/kg/day Initial SIM Dosage vs Placebo



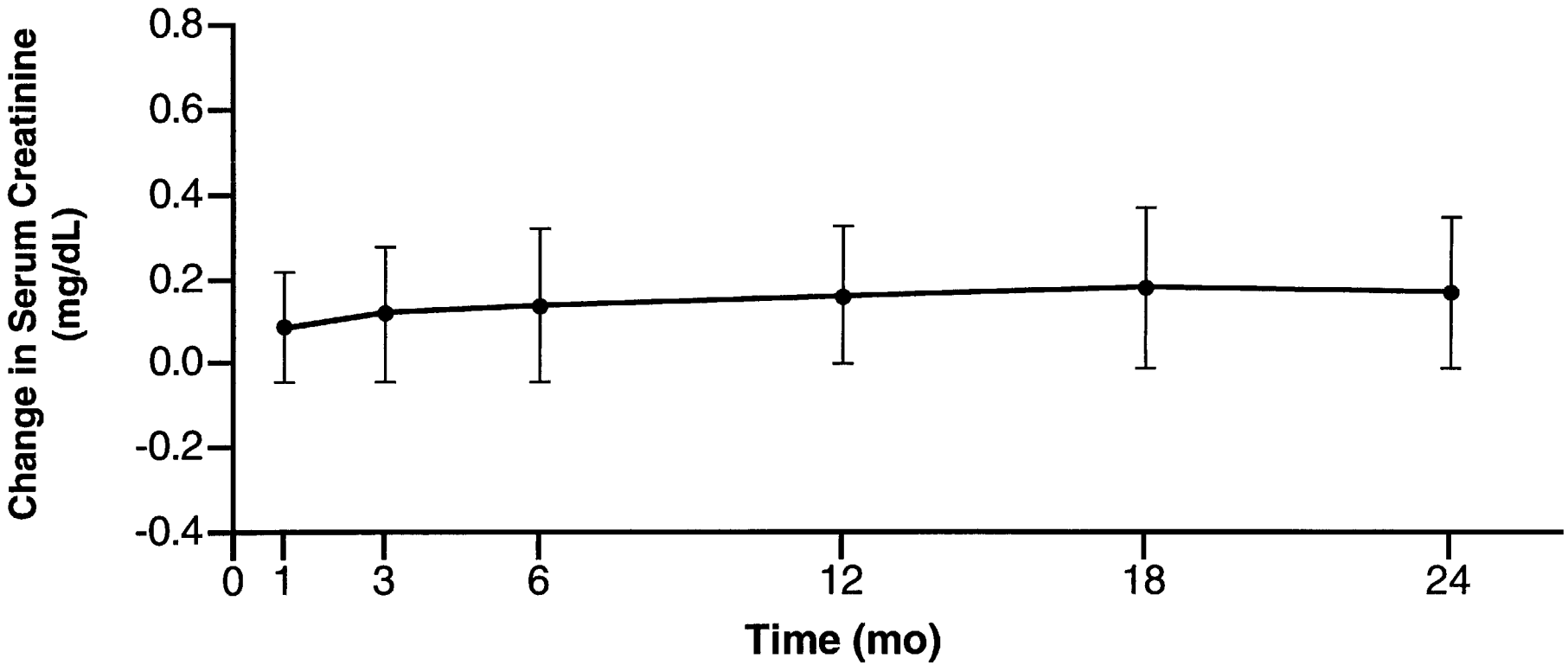
CHANGE FROM BASELINE IN SERUM CREATININE OVER 2 YEARS OF CsA TREATMENT

Studies 651, 652, 653, 2008, 2401, and 2404 (n=575)



Mean, SD, (n).
*Maximum dosage.

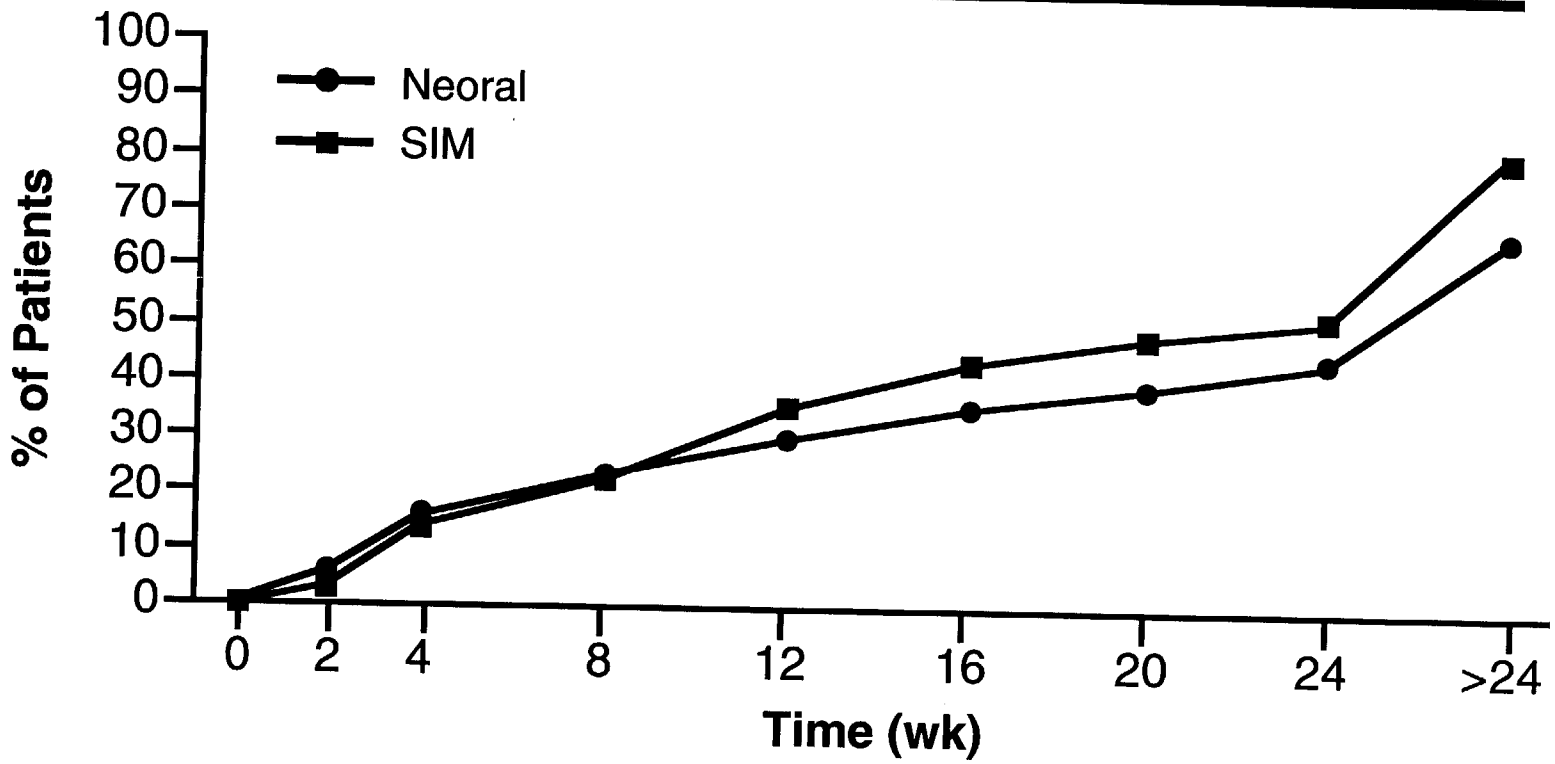
CHANGE FROM BASELINE IN SERUM CREATININE OVER TIME IN PATIENTS REMAINING ON CsA TREATMENT* AT 2 YEARS
Studies 651, 652, 653, 2008, 2401, and 2404 (n=129)



Mean, SD.
*Patients with 2.5-4.0 mg/kg/day maximum SIM dosage.

ON-DRUG SERUM CREATININE REVERSIBILITY*

Cumulative Rate of Reversal†

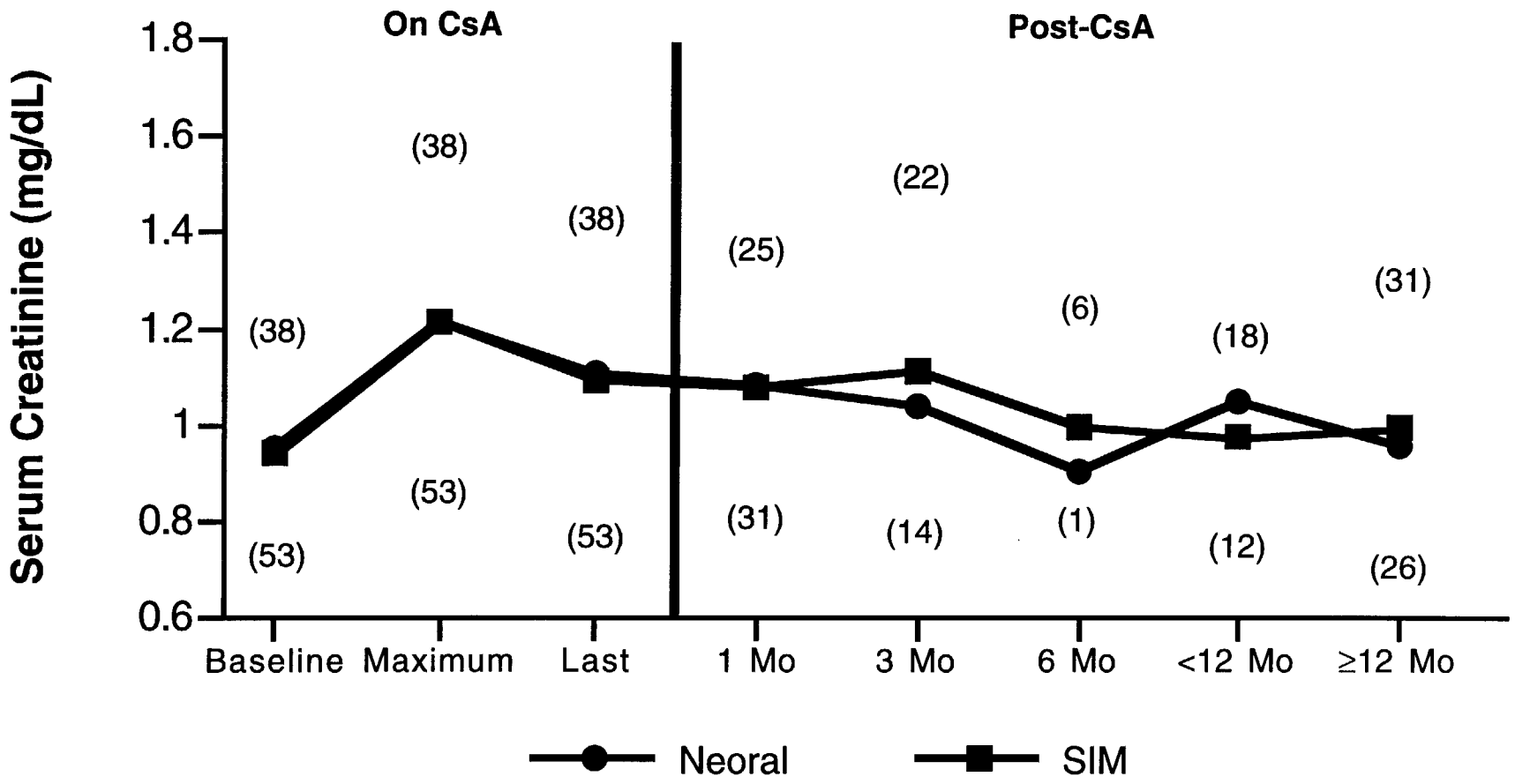


Neoral	No. of Reversals / No. of Patients at Risk	5/82	8/72	5/60	4/50	3/43	2/35	2/29	10/27
SIM	No. of Reversals / No. of Patients at Risk	2/77	8/65	5/55	7/45	4/33	2/29	1/20	9/16

*Patient population consists of those patients with serum creatinine increase ≥30% above baseline.
†Serum creatinine increase above baseline returning to <30% and staying <30%.

SERUM CREATININE AFTER DISCONTINUATION OF CsA TREATMENT

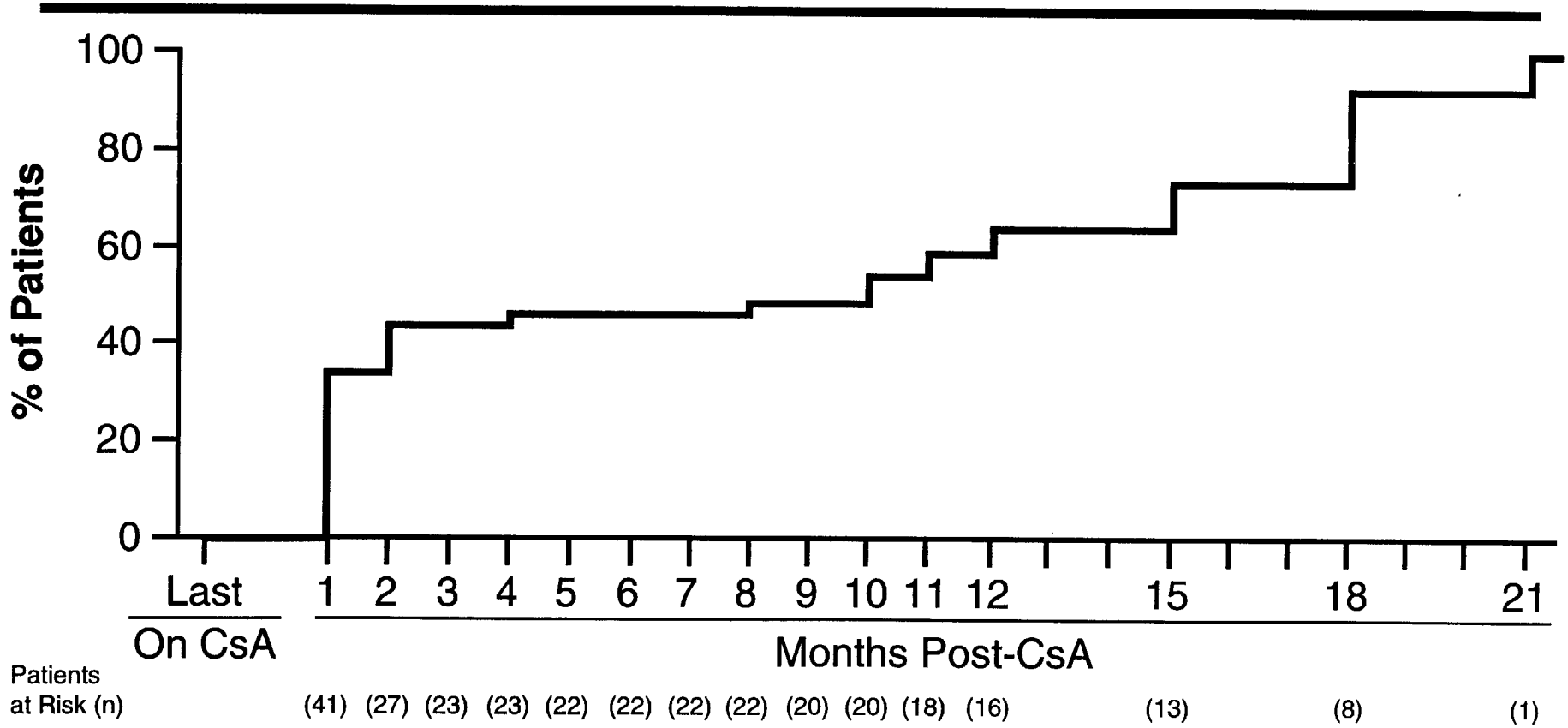
Follow-Up Population—Study 302



Mean, SD, (n).

CUMULATIVE INCIDENCE OF REVERSED SERUM CREATININE ELEVATION* POST–CsA TREATMENT AMONG PATIENTS WITH ≥30% INCREASE FROM BASELINE

Follow-Up Population



* Serum creatinine <15% increased above baseline among patients who had a ≥30% increase above baseline any time on CsA treatment, with all subsequent values <30% above baseline.

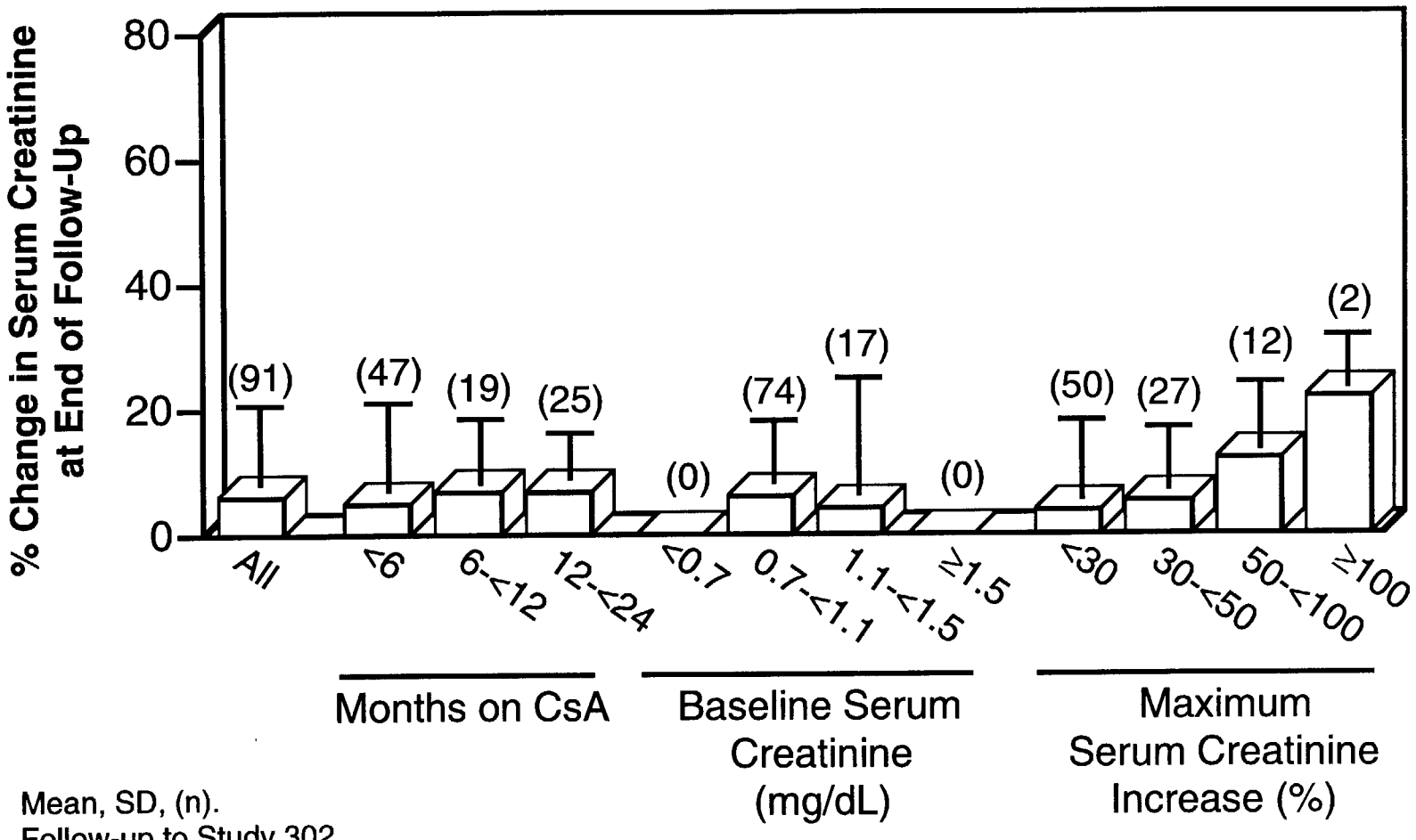
Follow-up of Study 302.

REVERSIBILITY ANALYSIS
Study 302

- Reversibility was defined as serum creatinine returning to <15% above baseline with all subsequent values <30% above baseline
- Logistic regression revealed that none of the following variables has a significant impact on reversibility
  - Baseline serum creatinine
  - Maximum dosage and duration of exposure
  - Age
  - Sex
  - Body weight
  - Concomitant NSAID use
- The following variable was found to have a significant impact on reversibility
  - Maximum on-treatment serum creatinine

PERCENT CHANGE IN SERUM CREATININE ABOVE BASELINE AT END POINT AFTER DISCONTINUATION OF CsA TREATMENT BY RISK FACTOR

Follow-Up Population (Neoral and SIM, N=91)



Mean, SD, (n).
Follow-up to Study 302.

CsA RENAL DYSFUNCTION IN RA PATIENTS
Summary

- Modest serum creatinine increase is common
- Serum creatinine increase is dose dependent
- Serum creatinine increase is stable over 2 years if dose is adjusted
- Reversible with appropriate dose decreases
- Largely reversible after discontinuation of CsA in most patients
  - 33/41 at risk had serum creatinine levels return to ≤15% elevation from baseline
  - 40/41 at risk had serum creatinine levels return to ≤30% elevation from baseline
  - 50 remaining patients did not develop a serum creatinine elevation ≥30% from baseline at any time
- Reversibility is partial in some patients when serum creatinine increase on treatment is >50%

RECOMMENDATIONS FOR NEORAL USE
Renal

- Obtain two baseline serum creatinine levels before initiating treatment
- Initiate Neoral at a dosage of 2.5 mg/kg/day
- Monitor serum creatinine every 2 weeks for the first 3 months, then monthly thereafter
- Reduce Neoral dosage by 25% to 50% if serum creatinine levels exceed 30% above baseline
- Increase frequency of monitoring if NSAIDs dose is increased or after initiation of new NSAID therapy
- Do not exceed Neoral dosage of 4 mg/kg/day

HYPERTENSION

DEFINITIONS OF HYPERTENSION

- Adverse event reporting
- WHO definition (1984)
  - Systolic blood pressure >160 mm Hg*
  - Diastolic blood pressure >95 mm Hg*
- **Fifth Joint National Committee definition (1993)**
  - **Systolic blood pressure ≥140 mm Hg†**
  - **Diastolic blood pressure ≥90 mm Hg†**

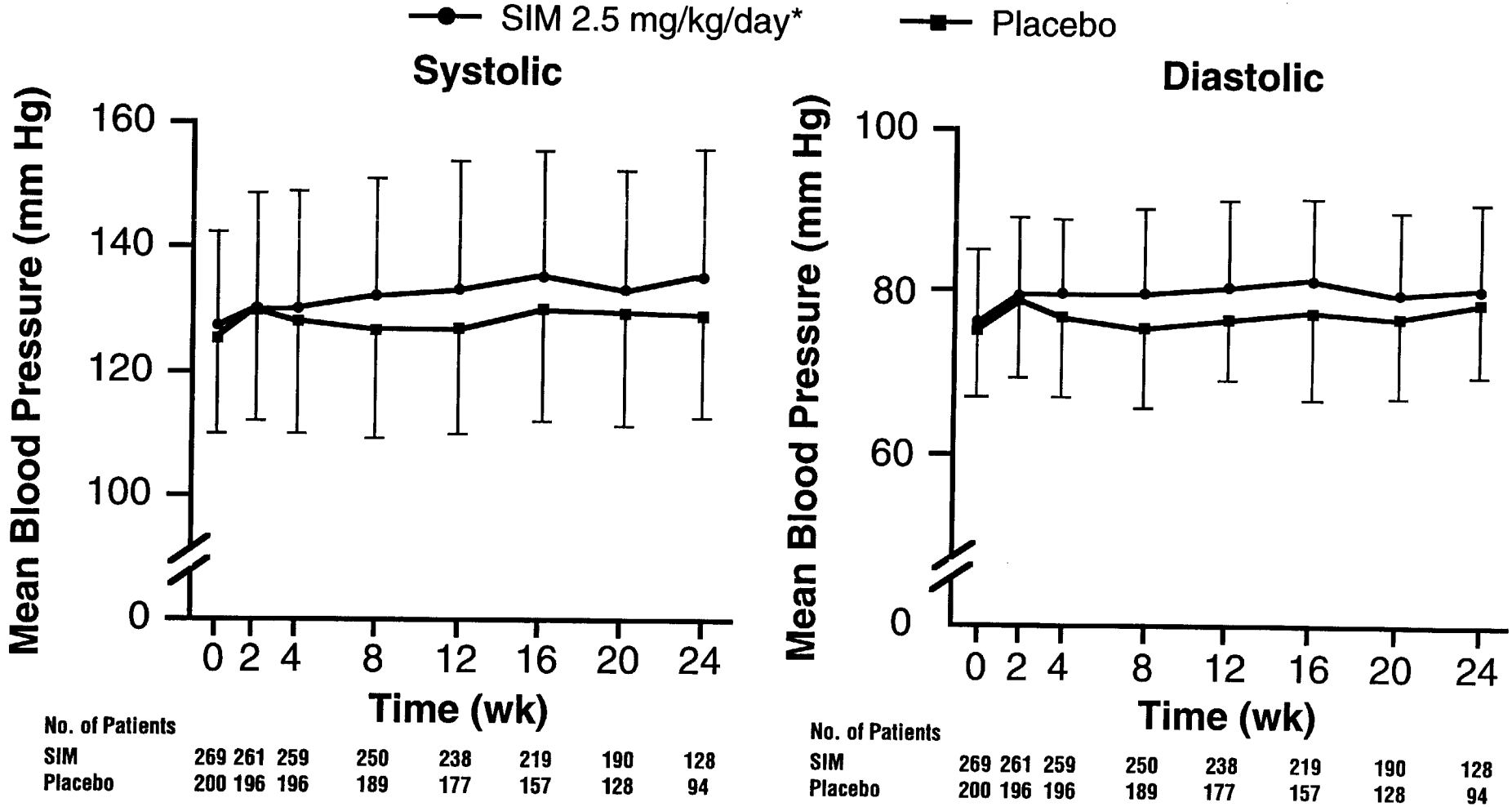
*At ≥2 visits, not necessarily consecutive.
†At ≥2 consecutive visits.

POTENTIAL MECHANISM OF ACTION FOR CsA-INDUCED HYPERTENSION AND TREATMENT RECOMMENDATIONS

- Leading causes of CsA-induced hypertension
  - **Intrarenal vasoconstriction**
  - Sympathetic nervous system stimulation
- Treatment recommendations
  - Renal vasodilator drugs such as calcium channel blockers

MEAN BLOOD PRESSURE

Studies 651, 652, and 2008 (Weeks 0 to 24)

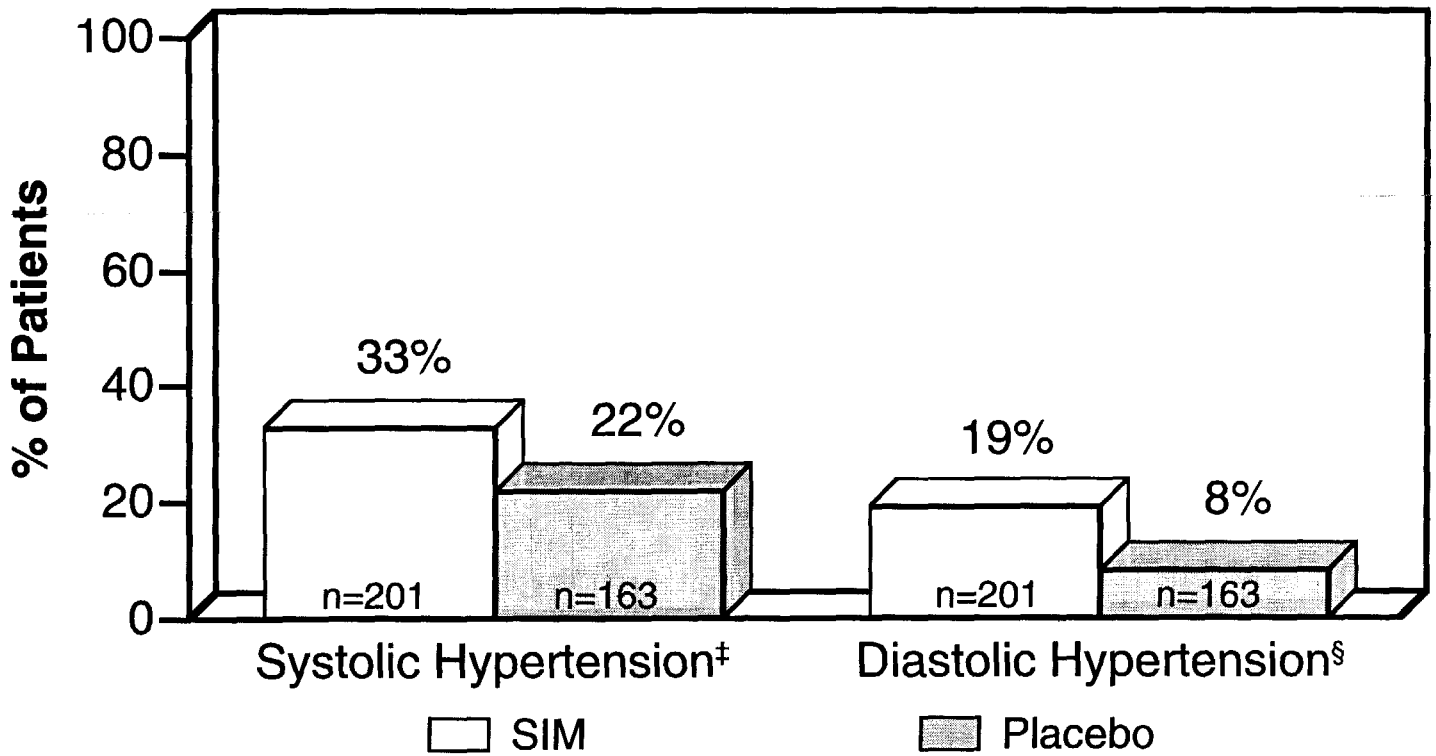


Mean, SD.

*Initial dosage.

CUMULATIVE INCIDENCE OF NEWLY OCCURRING HYPERTENSION*

Studies 651, 652, and 2008†—Week 24



*Excluding 68 SIM and 38 placebo patients with baseline systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.

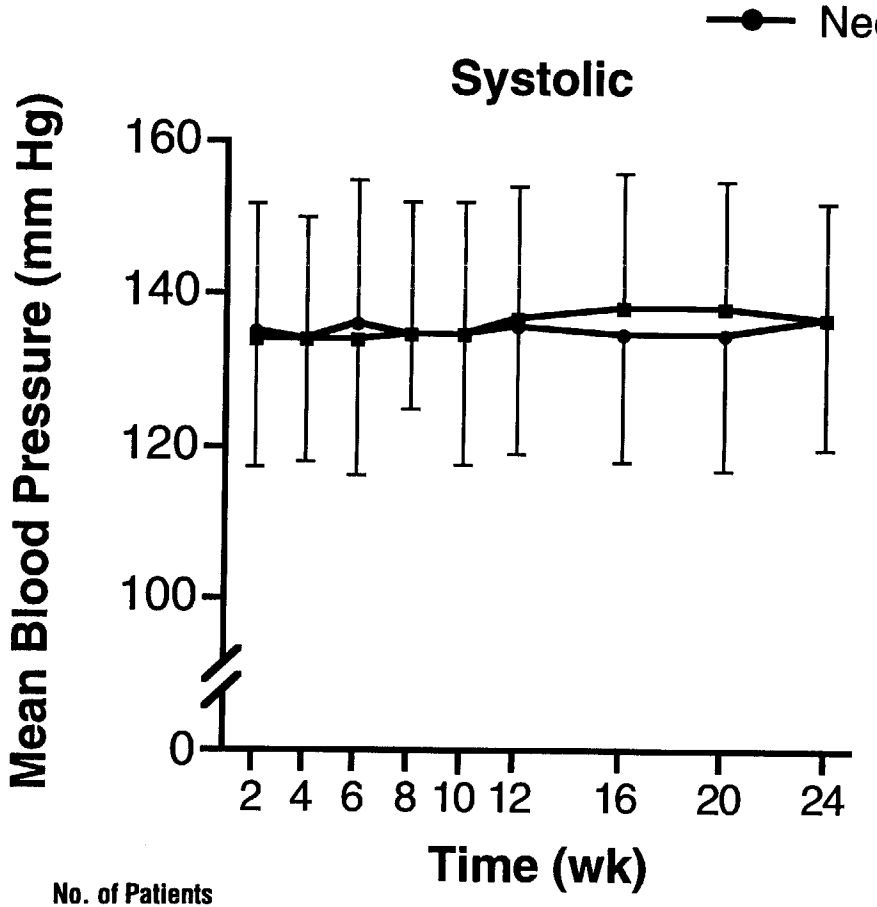
†Patients with 2.5 mg/kg/day initial dosage.

‡Systolic blood pressure ≥140 mm Hg at ≥2 consecutive visits.

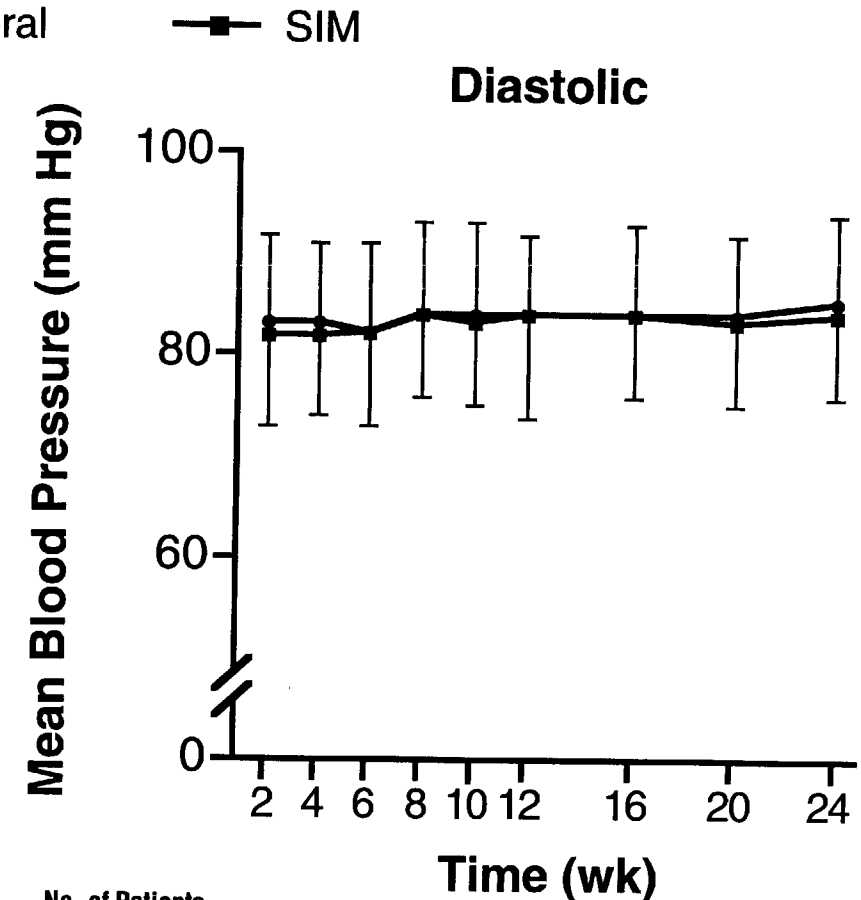
§Diastolic blood pressure ≥90 mm Hg at ≥2 consecutive visits.

MEAN BLOOD PRESSURE

Study 302 (Weeks 0 to 24)



No. of Patients									
SIM	141	146	136	143	125	133	121	113	97
Neoral	154	138	145	131	135	127	113	102	98



No. of Patients									
SIM	141	138	136	131	125	122	121	102	97
Neoral	154	146	145	143	135	133	113	113	98

Mean, SD.

PROTOCOL-STATED DIRECTIONS FOR ANTIHYPERTENSIVE INTERVENTION

Studies 651, 652, 654, 2008, and 302

- Studies 651, 652, and 654
  - If systolic blood pressure is >160 mm Hg or diastolic blood pressure is >95 mm Hg on two consecutive visits, introduce beta blocker
  - If after 1 month, hypertension is not controlled, reduce SIM dose by 50%
- Study 2008
  - If systolic blood pressure is >160 mm Hg or diastolic blood pressure is >95 mm Hg on two visits (most likely consecutive), introduce beta blocker
- Study 302
  - If diastolic blood pressure is >95 mm Hg on two consecutive visits, introduce calcium channel blocker or beta blocker and reduce CsA dose
  - If diastolic blood pressure is >110 mm Hg at any time, discontinue CsA

INTERVENTIONS FOR DEVELOPMENT OF NEWLY OCCURRING HYPERTENSION AND OUTCOME

Study 302

	Neoral (n=143)	SIM (n=155)
No. of patients developing systolic blood pressure >160 mm Hg and/or diastolic blood pressure >95 mm Hg at ≥2 consecutive visitis	18 (13%)	19 (12%)
No. of patients on antihypertensive medications	5	2
No. of patients requiring change of antihypertensive medications	2	0
No. of patients returning to normotensive	1	0
No. of patients requiring new antihypertensive medications	7	9
No. of patients returning to normotensive	5 (71%)	6 (67%)

INTERVENTIONS FOR DEVELOPMENT OF NEWLY OCCURRING HYPERTENSION AND OUTCOME

Studies 651, 652, 2008, and 654*

	Study 651 SIM (n=100)	Study 652 SIM (n=97)	Study 2008 SIM (n=72)	Study 654 SIM (n=74)
No. of patients developing systolic blood pressure >160 mm Hg and/or diastolic blood pressure >95 mm Hg at ≥2 consecutive visitis	10 (10%)	2 (2%)	20 (28%)	5 (7%)
No. of patients on baseline antihypertensive medications	4	0	0	1
No. of patients requiring change of antihypertensive medications	4	–	0	1
No. of patients returning to blood pressure <160/95 mm Hg	2	–	–	0
No. of patients requiring new antihypertensive medications	4	2	9	0
No. of patients returning to normotensive	3 (75%)	0 (0%)	7 (78%)	0 (0%)

*2.5 mg/kg/day initial dosage.

RISK FACTORS* FOR THE DEVELOPMENT OF NEWLY OCCURRING HYPERTENSION

Studies 651, 652, 2008, and 654

Blood Pressure at Baseline	Definition of Hypertension	Significant† Risk Factors
SBP <140 mm Hg	SBP ≥140 mm Hg‡	Baseline SBP SIM
DBP <90 mm Hg	DBP ≥90 mm Hg‡	Baseline DBP SIM
SBP ≤160 mm Hg	SBP >160 mm Hg§	Baseline SBP SIM
DBP ≤95 mm Hg	DBP >95 mm Hg§	Baseline DBP SIM

*Logistic regression. Variables assessed: age (≤65 yr, >65 yr), steroid use, NSAID use, baseline blood pressure, treatment group.

†$P<0.05$.

‡At ≥2 consecutive visits.

§At ≥2 visits.

RISK FACTORS* FOR THE DEVELOPMENT OF NEWLY OCCURRING HYPERTENSION

Study 302

Blood Pressure at Baseline	Definition of Hypertension	Significant† Risk Factors
SBP ≤160 mm Hg DBP ≤95 mm Hg	SBP >160 mm Hg‡ DBP >95 mm Hg‡	Age (>65 yr) None
SBP <140 mm Hg DBP <90 mm Hg	SBP ≥140 mm Hg§ DBP ≥90 mm Hg§	Age (>65 yr) Baseline blood pressure
SBP ≥140 mm Hg DBP ≥90 mm Hg	SBP rise ≥20 mm Hg DBP rise ≥10 mm Hg	None None

*Logistic regression. Variables assessed: age (≤65 yr, >65 yr), steroid use, NSAID use, baseline blood pressure, baseline antihypertensive medications, treatment group.

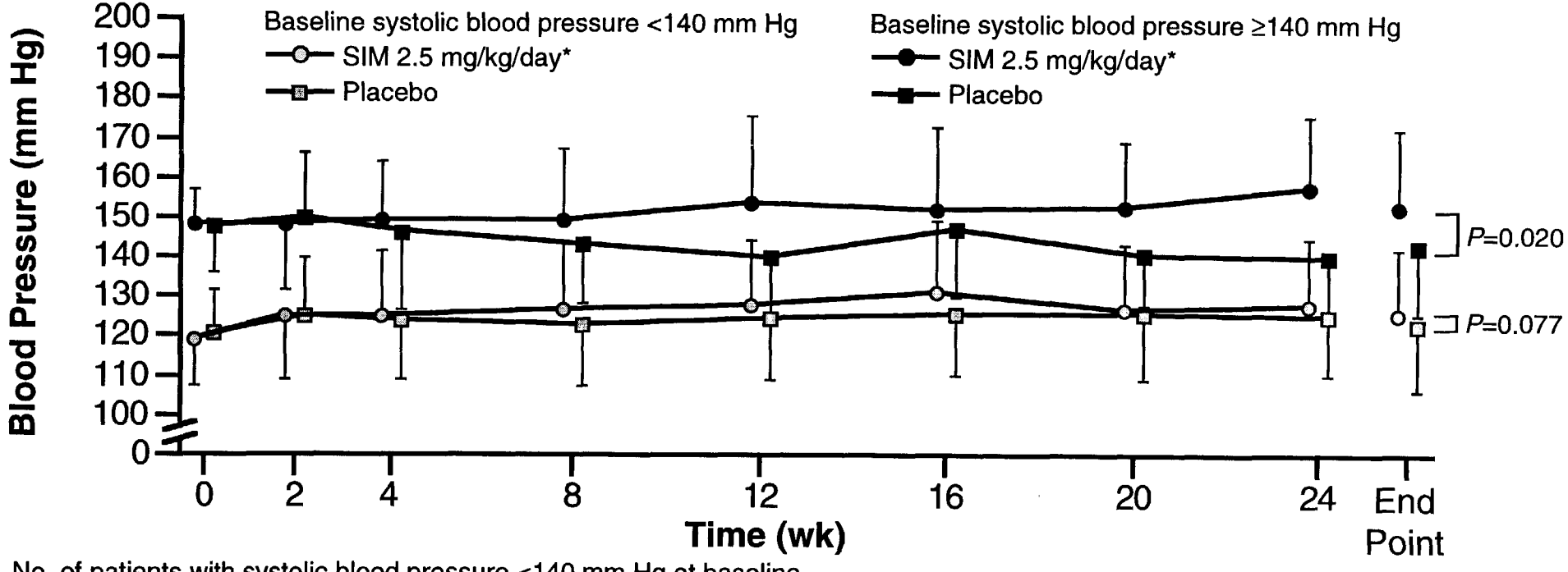
†$P \leq 0.05$.

‡At ≥2 visits.

§At ≥2 consecutive visits.

MEAN SYSTOLIC BLOOD PRESSURE IN PATIENTS WITH AND WITHOUT BASELINE SYSTOLIC BLOOD PRESSURE ≥140 mm Hg

Studies 651, 652, and 2008



No. of patients with systolic blood pressure <140 mm Hg at baseline

SIM	203	199	197	193	186	169	146	97	202
Placebo	164	161	161	157	146	130	105	72	165

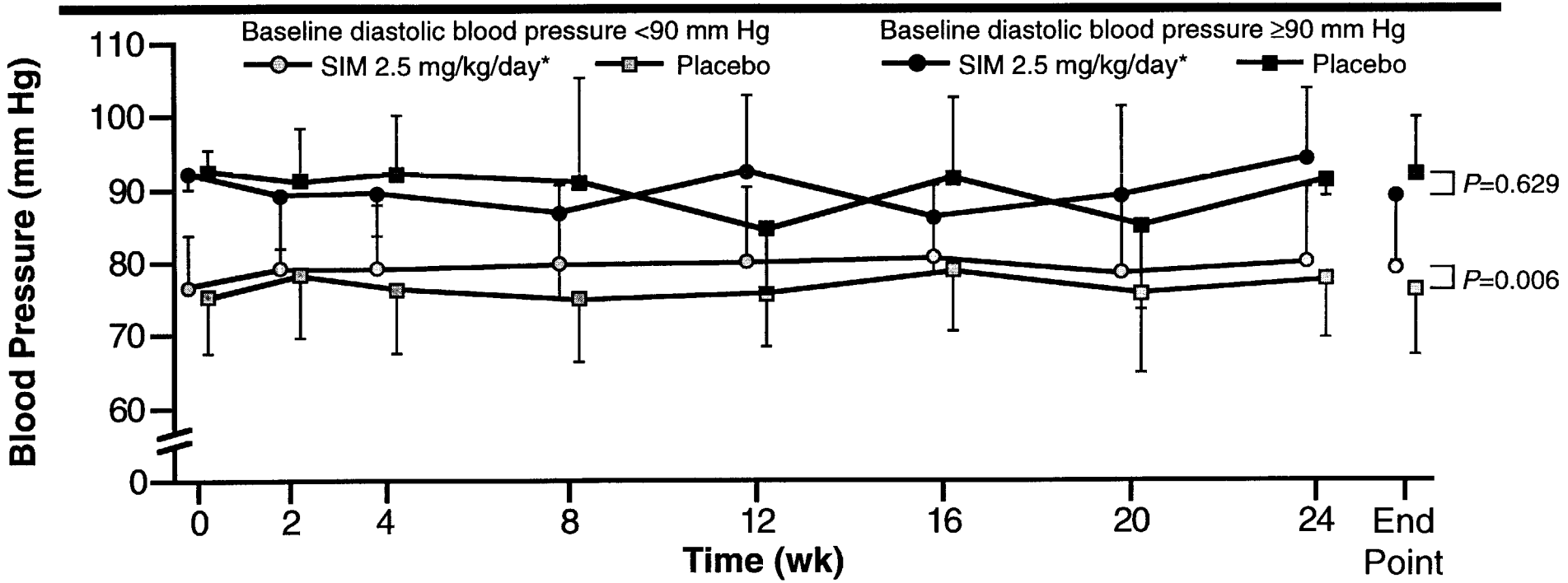
No. of patients with systolic blood pressure ≥140 mm Hg at baseline

SIM	66	62	62	57	52	50	44	31	64
Placebo	36	35	35	32	31	27	23	22	35

Mean, SD. *Initial dosage.

MEAN DIASTOLIC BLOOD PRESSURE IN PATIENTS WITH AND WITHOUT BASELINE DIASTOLIC BLOOD PRESSURE ≥90 mm Hg

Studies 651, 652, and 2008



No. of patients with diastolic blood pressure <90 mm Hg at baseline

SIM	251	244	242	234	223	204	175	116	249
Placebo	190	186	186	180	168	150	122	88	190

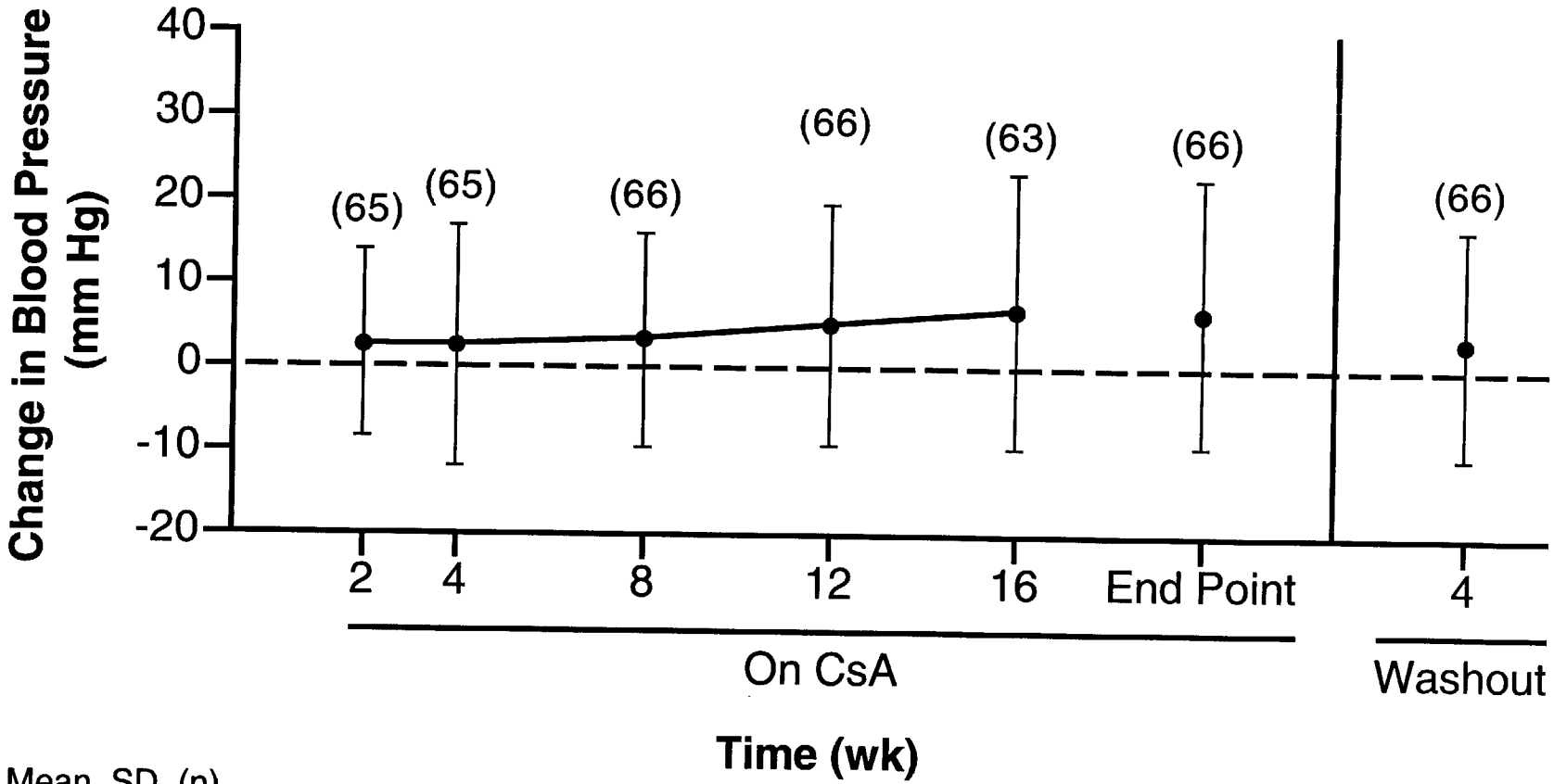
No. of patients with diastolic blood pressure ≥90 mm Hg at baseline

SIM	18	17	17	16	15	15	15	12	17
Placebo	10	10	10	9	9	7	6	6	10

Mean, SD. *Initial dosage.

REVERSIBILITY OF HYPERTENSION POST–CsA TREATMENT

Change in Systolic Blood Pressure—Studies 651 and 652*

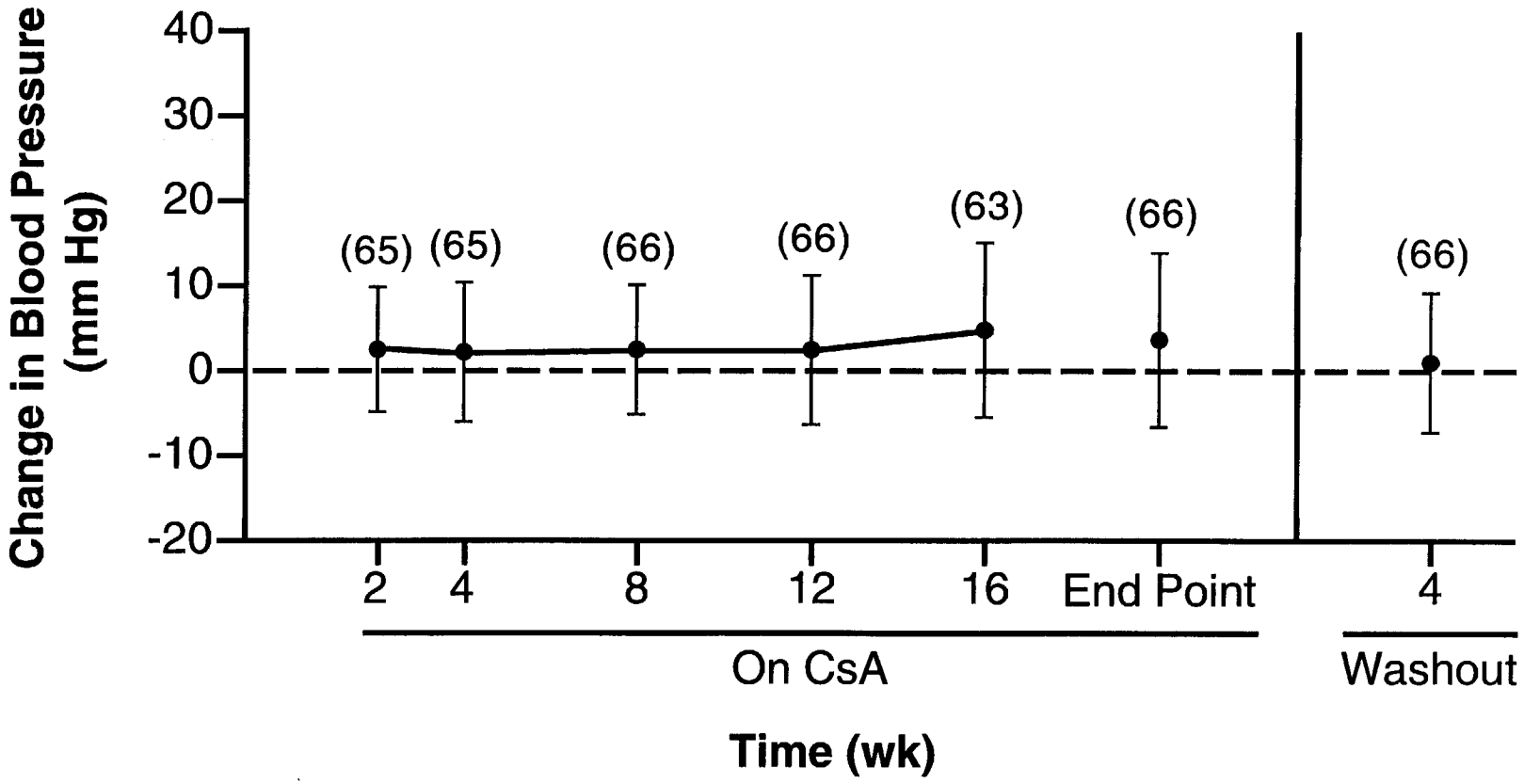


Mean, SD, (n).

*Patients with 2.5-5.49 mg/kg/day maximum SIM dosage and remaining at washout week 4.

REVERSIBILITY OF HYPERTENSION POST–CsA TREATMENT

Change in Diastolic Blood Pressure—Studies 651 and 652*



Mean, SD, (n).

*Patients with 2.5-5.49 mg/kg/day maximum SIM dosage and remaining at washout week 4.

HYPERTENSION SUMMARY

- The incidence of newly occurring hypertension (systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg) was 11% higher in CsA-treated patients than in placebo-treated patients
- Blood pressure could be maintained at levels <160/95 mm Hg in the majority of patients who received treatment (intervention level, 160/95 mm Hg)
- Patients who are ≥65 years of age and have higher baseline blood pressure are at greater risk for an increase in blood pressure

RECOMMENDATIONS FOR NEORAL USE
Hypertension

- Patients should have blood pressure <140/90 mm Hg (controlled by antihypertensive medications, if necessary) before initiating Neoral therapy
- If blood pressure exceeds 140/90 mm Hg, antihypertensive medications (calcium channel blockers, beta blockers) should be initiated

LYMPHOMA

MALIGNANCIES OCCURRING DURING OR AFTER COMPLETION OF CsA TREATMENT IN CLINICAL TRIALS

Malignancy	N=1968
Basal cell	10
Breast	4
Lung	4
Prostate	4
Colon	3
Lymphoma	**3**
Squamous cell	3
Cervical	2
Melanoma	2
Stomach	2
Thyroid	2
Brain	1
Leukemia	1
Pancreas	1
Vocal cord	1
Total	43

MALIGNANT LYMPHOMAS IN CsA-TREATED RA PATIENTS

Date of Study/ CsA Treatment	Patient*	Duration of SIM Treatment	Dosage of SIM	Previous Medication	Concomitant Medication	Comments
1985	62-yr-old male with B-cell lymphoma	46 mo	Up to 5 mg/kg/day	Unknown	Unknown	Patient died
1991	56-yr-old female with non-Hodgkin's lymphoblastic lymphoma (stage III)	12 mo	Up to 2.3 mg/kg/day	Unknown	Sulindac	Combination chemotherapy initiated, outcome unknown
1992	49-yr-old female with B-cell lymphoma	10 mo	3.0 mg/kg/day	MTX	Unknown	Chemotherapy initiated, outcome unknown
1993	60-yr-old male with EBV+ Hodgkin's disease (mixed cellularity stage IA)	3 mo	250 mg/day	Sulfasalazine, azathioprine	MTX	Chemotherapy initiated, outcome unknown
1995	57-yr-old female with B-cell lymphoma	5 mo	250 mg/day	D-penicillamine, prednisone	Prednisone	Patient developed lymphadenopathy 1 year after discontinuing CsA; chemotherapy initiated, outcome unknown
1997	55-yr-old male with Hodgkin's disease (mixed cellularity stage IVA)	11 mo	250 mg/day	MTX, gold	MTX, gold, prednisone	Outcome unknown

*One spontaneous report of a 67-yr-old male CsA-treated patient developing lymphoproliferative disorder after 7 mo of treatment not included.

RECOMMENDATIONS FOR NEORAL USE
Lymphoma

- Patients should be thoroughly evaluated for the presence of malignancy before initiating and during treatment with Neoral
- Patients with malignancy should not receive Neoral
- The risk of lymphoma with CsA does not appear increased over that expected for RA patients or for RA patients treated with other immunosuppressants

SAFETY SUMMARY

- CsA therapy is most commonly associated with the following adverse events
  - Serum creatinine increase, nausea, abdominal pain, headache, hypertrichosis
- No difference was seen in incidence of clinically notable abnormalities between SIM and placebo

SAFETY SUMMARY (cont)

- Renal
  - Elevations of serum creatinine occur commonly while CsA-associated renal structural changes occur rarely
  - Elevations in serum creatinine are reversible after decrease in dose in the majority of patients
  - Structural changes are infrequent if
    - CsA dosage is <5 mg/kg/day
    - Serum creatinine is maintained <30% above baseline

SAFETY SUMMARY (cont)

- Hypertension
  - The incidence of newly occurring hypertension (≥140/90 mm Hg) was 11% higher in CsA-treated patients than in placebo-treated patients
    - It can be managed by introduction of pharmacologic therapy (calcium channel blockers, beta blockers) in the majority of cases
  - Patients on treatment for hypertension who develop worsening hypertension can be managed with appropriate alterations of dose or introduction of new therapy
- Lymphoma
  - The risk of lymphoma with CsA therapy is not increased over that expected for RA patients or for RA patients treated with other immunosuppressants
- Patients have been safely maintained on CsA therapy for up to 2 years

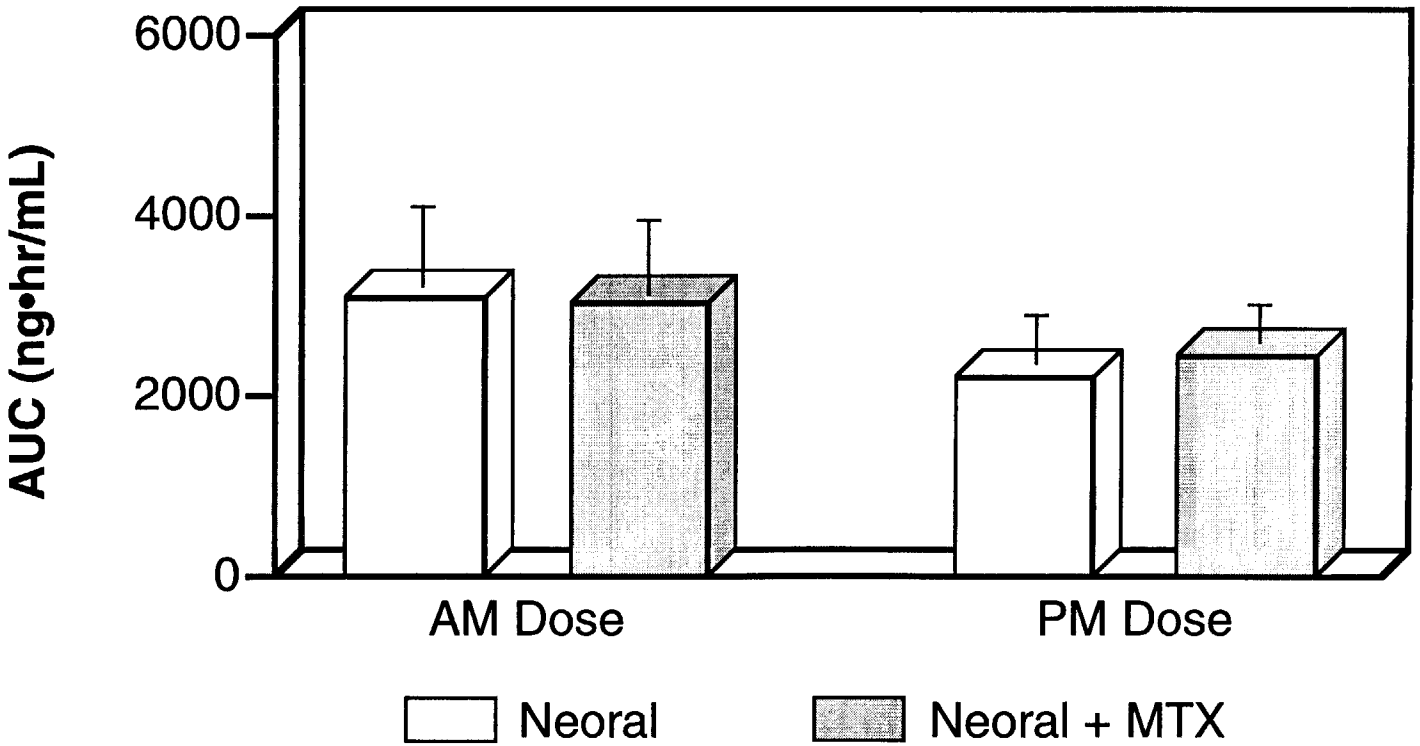
NEORAL AND MTX COMBINATION

STUDY 351

- Study objectives
  - Assess the pharmacokinetics of MTX, establish the multiple-dose pharmacokinetics of CsA after administration of Neoral, and assess possible changes in the pharmacokinetics of CsA and MTX, when the drugs are coadministered, compared to their pharmacokinetics after administration alone in patients with RA
- Study design
  - Open-label study
  - 30 patients with RA
  - Dosages: individualized MTX dosing on days 1 and 23; Neoral, 1.5 mg/kg q12h on days 8 to 23
  - Formulations: Neoral soft gelatin capsules (25 and 100 mg); Rheumatrex (methotrexate) tablets (2.5 mg)
  - PK profiles of MTX and 7-OH MTX in plasma and urine on days 1 to 3 and 23 to 25; PK profiles of CsA on days 22 and 23

EFFECT OF MTX ON NEORAL EXPOSURE IN RA PATIENTS

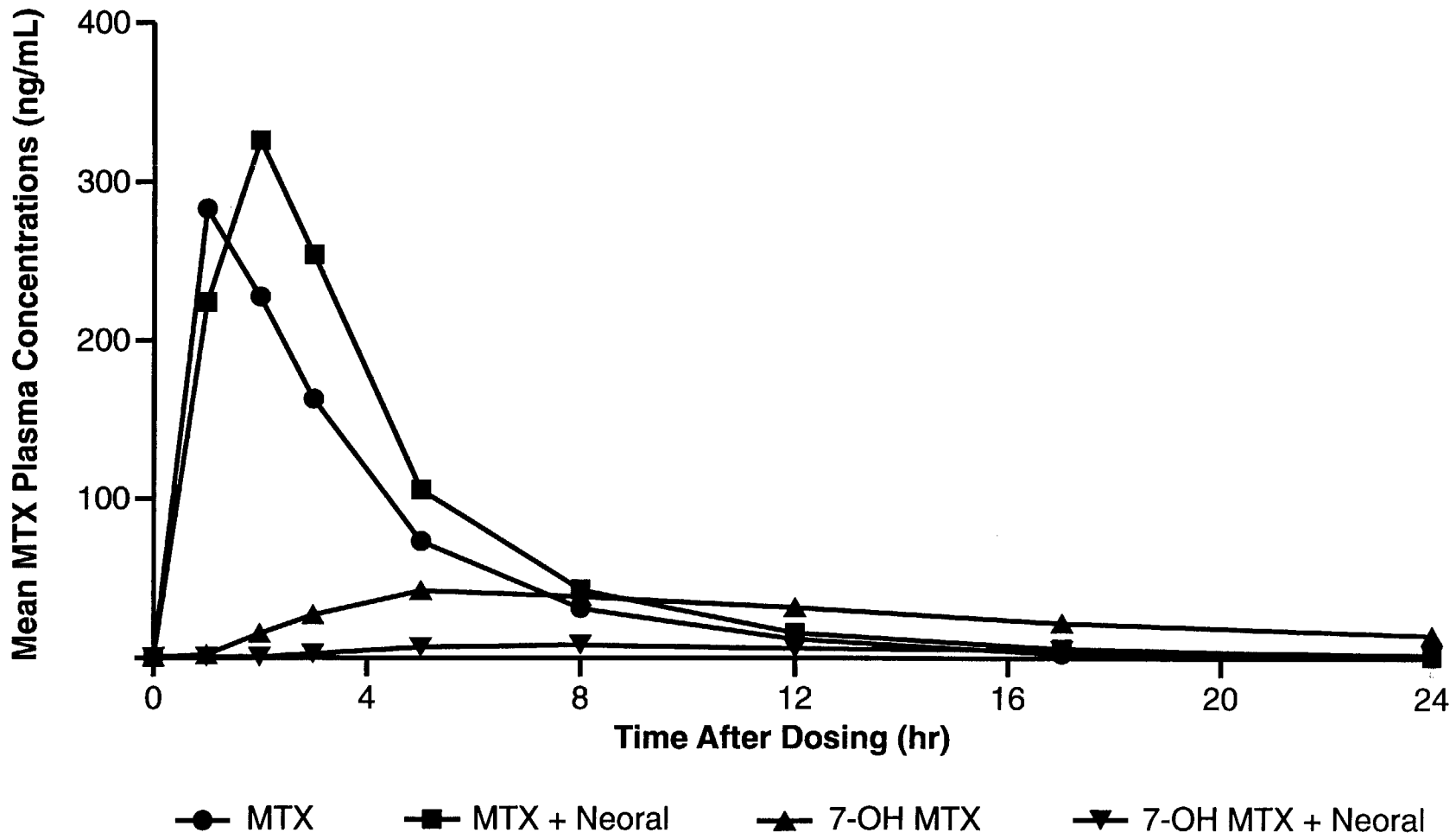
Study 351—AUC



Mean, SD.

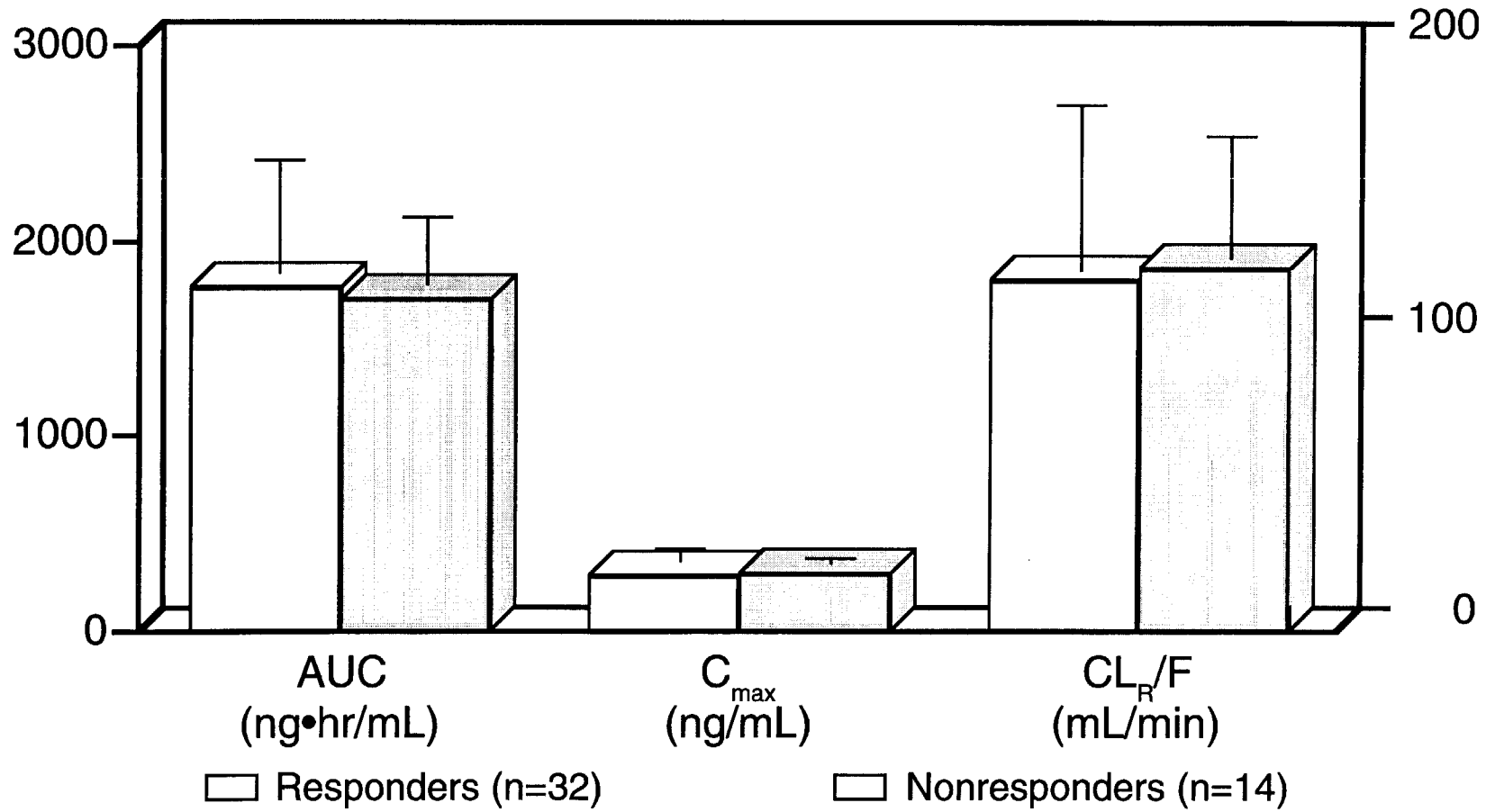
MEAN MTX AND 7-OH MTX PLASMA LEVELS IN RA PATIENTS

Study 351



NO CORRELATION BETWEEN MTX EFFICACY AND PK

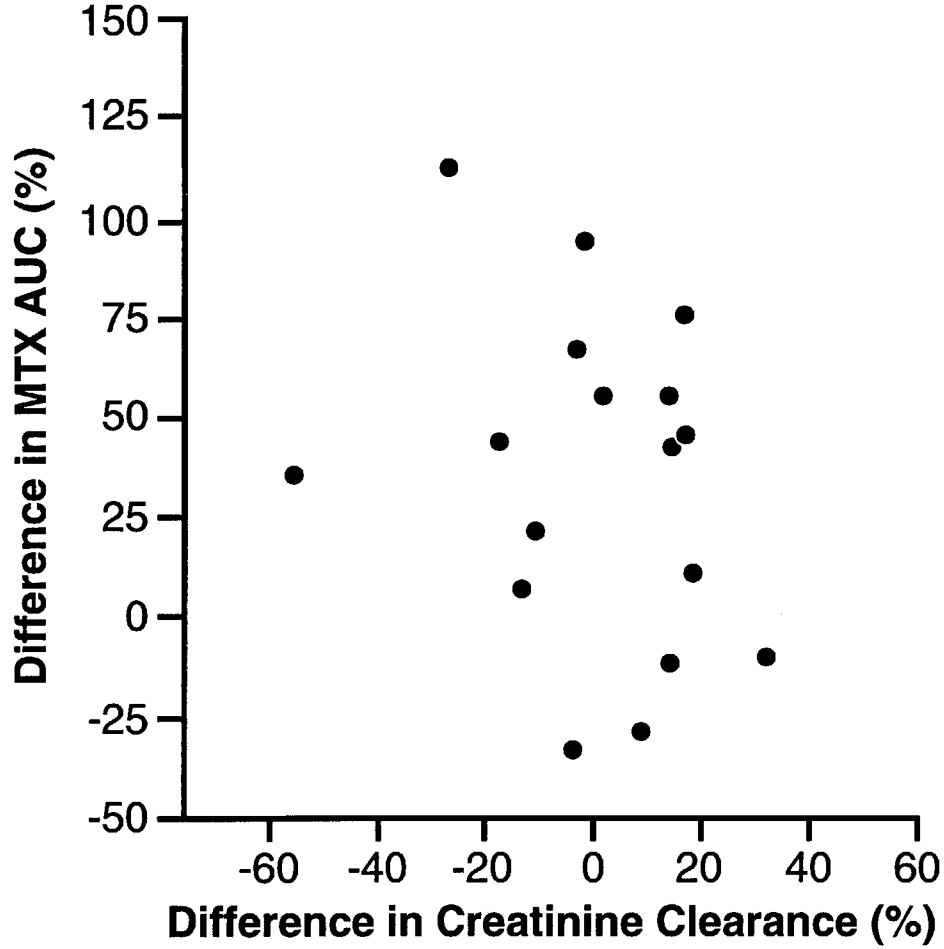
Responders vs Nonresponders



Lafforgue P et al. *J Rheumatol.* 1995;22:844.

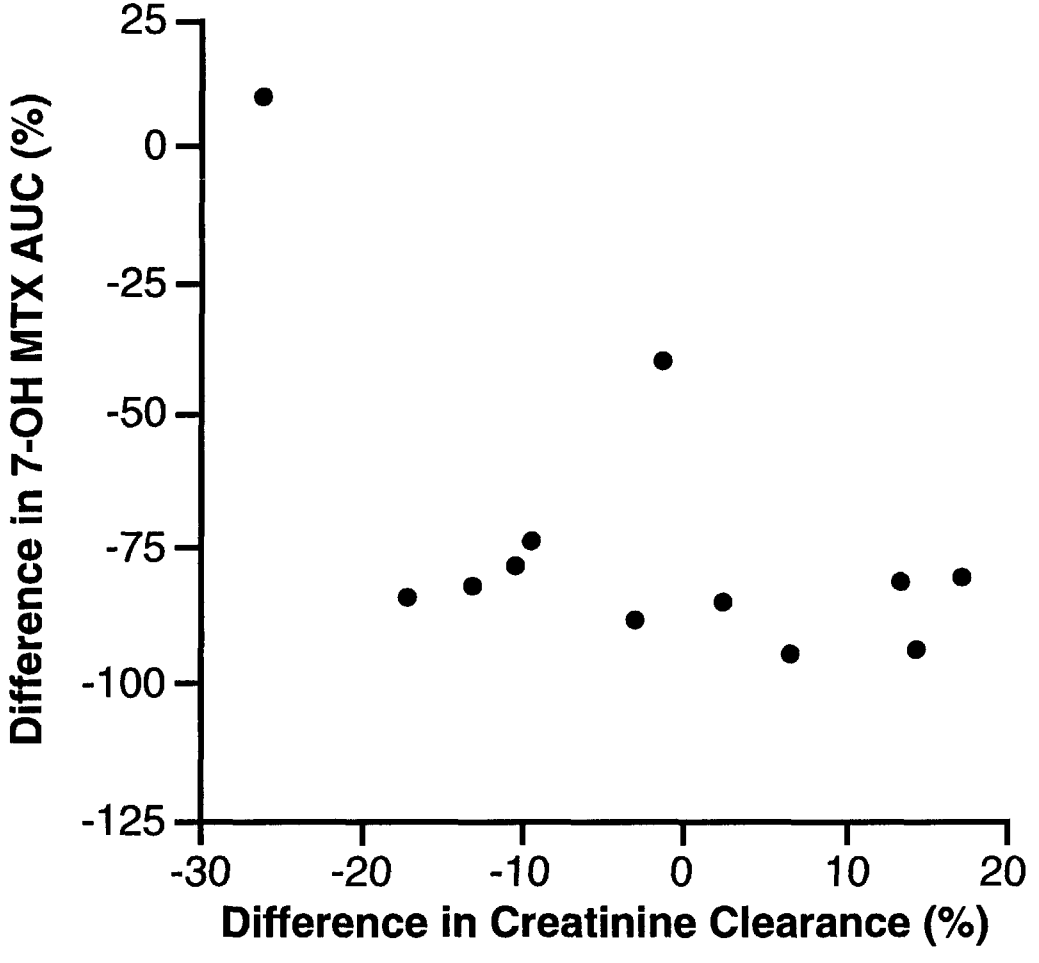
RELATIONSHIP OF DIFFERENCE IN CREATININE CLEARANCE AND DIFFERENCE IN MTX AUC

Study 351



RELATIONSHIP OF DIFFERENCE IN CREATININE CLEARANCE AND DIFFERENCE IN 7-OH MTX AUC

Study 351



CsA/MTX INTERACTION

- Combination CsA + MTX is associated with mean 30% increase in MTX AUC and a mean 75% decrease in 7-OH MTX AUC
- In spite of apparent decreased clearance of MTX, plasma levels do not persist beyond 24 hours
- No correlation is seen between change in creatinine clearance and change in bioavailability of MTX or 7-OH MTX
- No correlation is seen between MTX pharmacokinetic parameters and clinical response

ADVERSE EVENTS OCCURRING IN ≥5% OF SIM PATIENTS IN STUDY 651 WITH CORRESPONDING RATES IN OTHER GROUPS

Percentage of Patients

	Study 651		Study 654	
Adverse Event	**SIM (n=101) %**	**MTX (n=96) %**	**SIM + MTX (n=74) %**	**Placebo + MTX (n=73) %**
Nausea	24	17	24	15
Abdominal pain	20	18	15	7
Rash	10	12	9	7
Hypertension	15	6	16	12
Canker sores	6	14	16	12
Headache	15	4	22	11
Diarrhea	12	6	18	15
Vomiting	12	6	14	7
Dizziness	10	6	7	3
Cold symptoms	6	9	–	–
Back pain	8	5	7	5
Fatigue	7	3	8	12

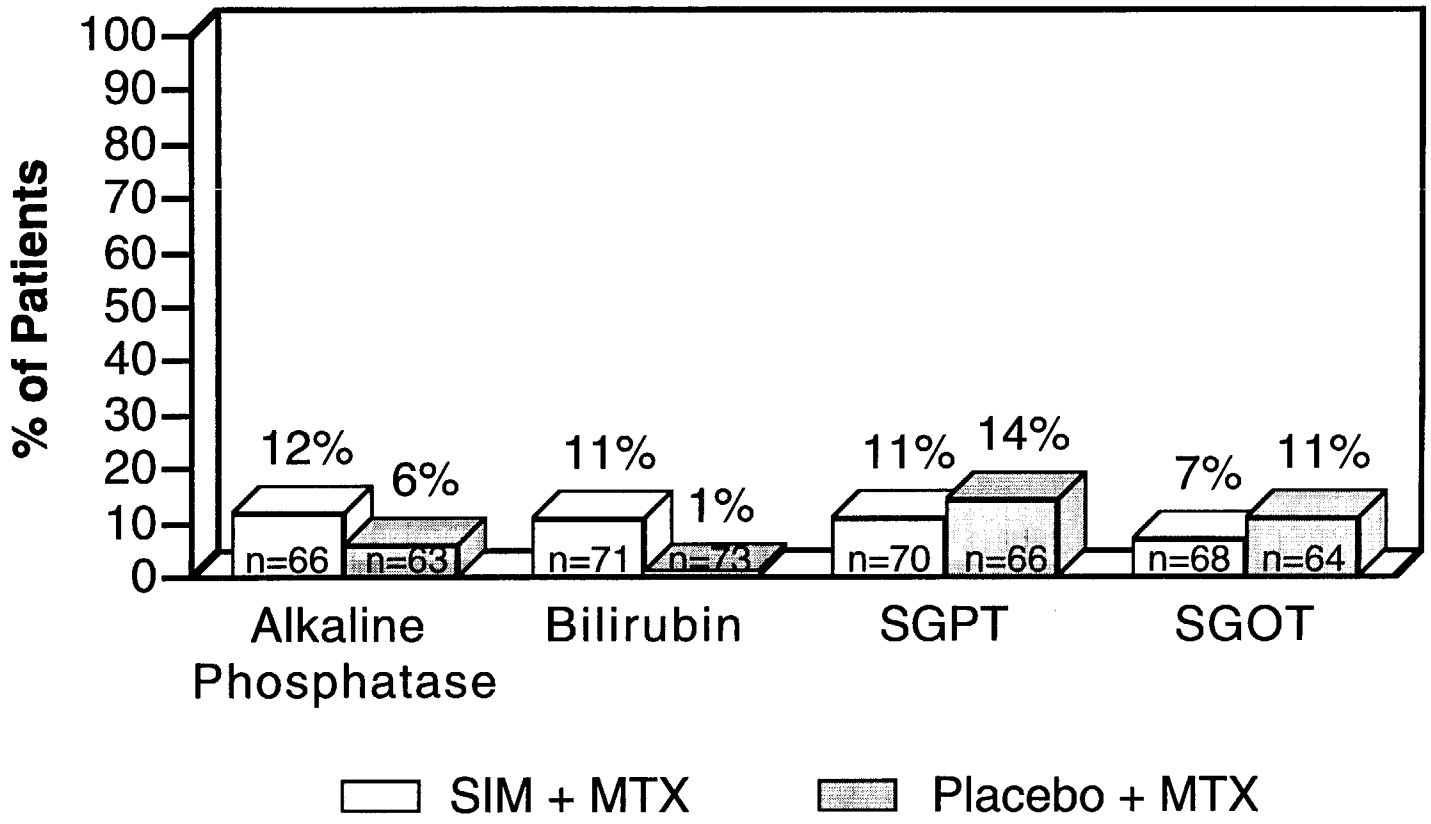
CUMULATIVE INCIDENCE OF CLINICALLY SIGNIFICANT LABORATORY ABNORMALITIES

Combination Study SIM and MTX—Percentage of Patients

Parameter	SIM + MTX (n=74) %	Placebo + MTX (n=73) %
Hematology		
Platelets <100,000/mm^3	0	0
Hemoglobin <9.5 g/dL	3	3
Biochemistry		
Serum creatinine ≥30% above baseline	61	21
Serum creatinine ≥50% above baseline	30	9
Uric acid >9.5 mg/dL	6	2
Magnesium <0.97 mg/dL	0	0
SGOT ≥3 × ULN	2	1
SGPT ≥3 × ULN	2	3

INCIDENCE OF NEWLY OCCURRING LIVER FUNCTION ABNORMALITIES* DURING 24-WEEK TREATMENT PERIOD†

Study 654—Percentage of Patients



*≥1 × ULN.

†Extension patients not included.

CONCLUSION

- Although a pharmacokinetic interaction was observed between MTX and CsA, results from a 6-month trial in which both drugs were coadministered failed to reveal any adverse clinical implications

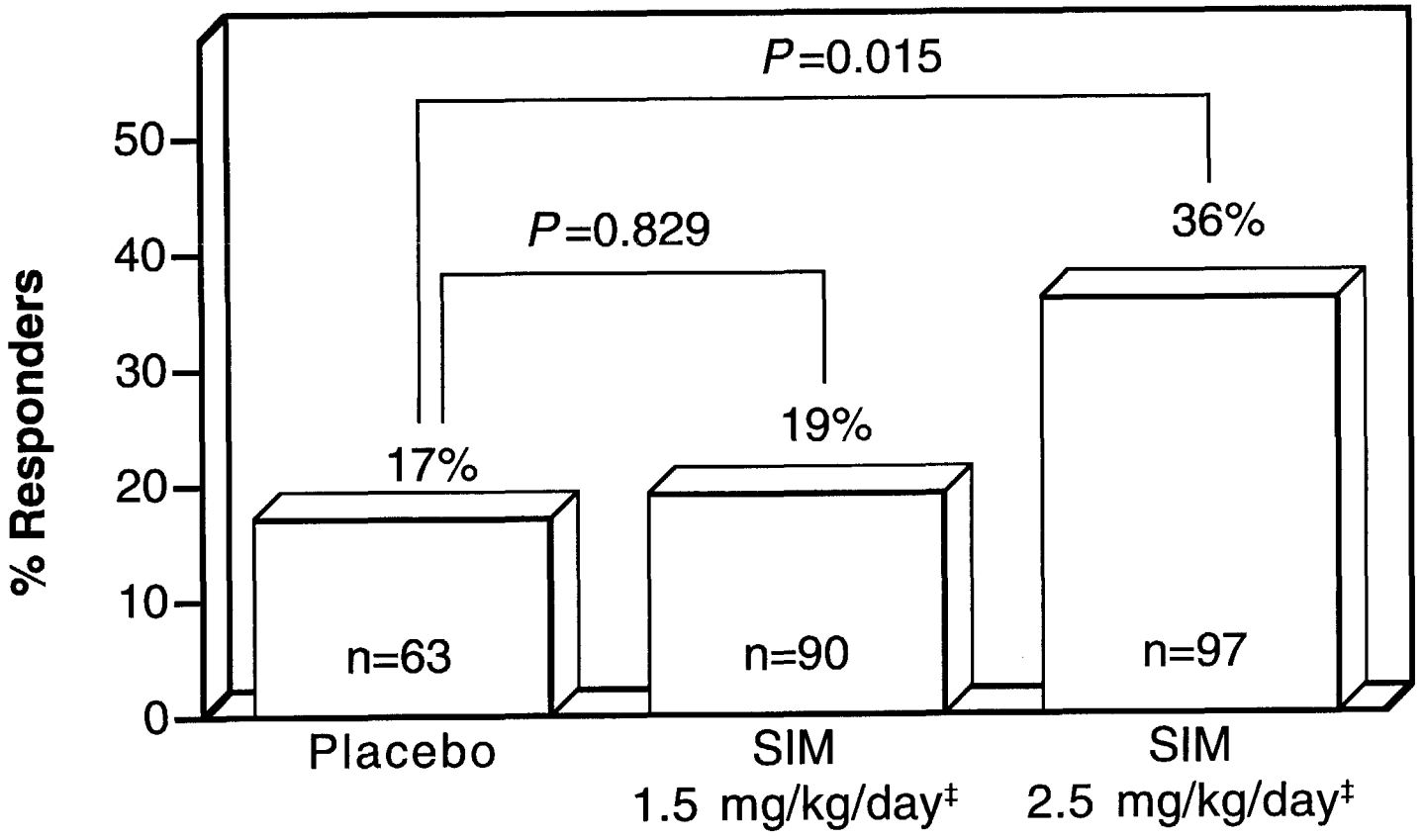
DOSING

DOSING RECOMMENDATIONS

- Initiate Neoral at 2.5 mg/kg/day
- After 4 to 8 weeks, if insufficient clinical benefit is seen and tolerability is good
  - Increase dosage by 0.5 to 0.75 mg/kg/day at 4-week intervals
  - Do not exceed a dosage of 4 mg/kg/day
  - Decrease dose by 25% to 50% decrements to control increased serum creatinine
  - If dose reductions do not control increased serum creatinine, discontinue Neoral

PERCENT RESPONDERS ACCORDING TO ACR CRITERIA* VS DOSAGE†

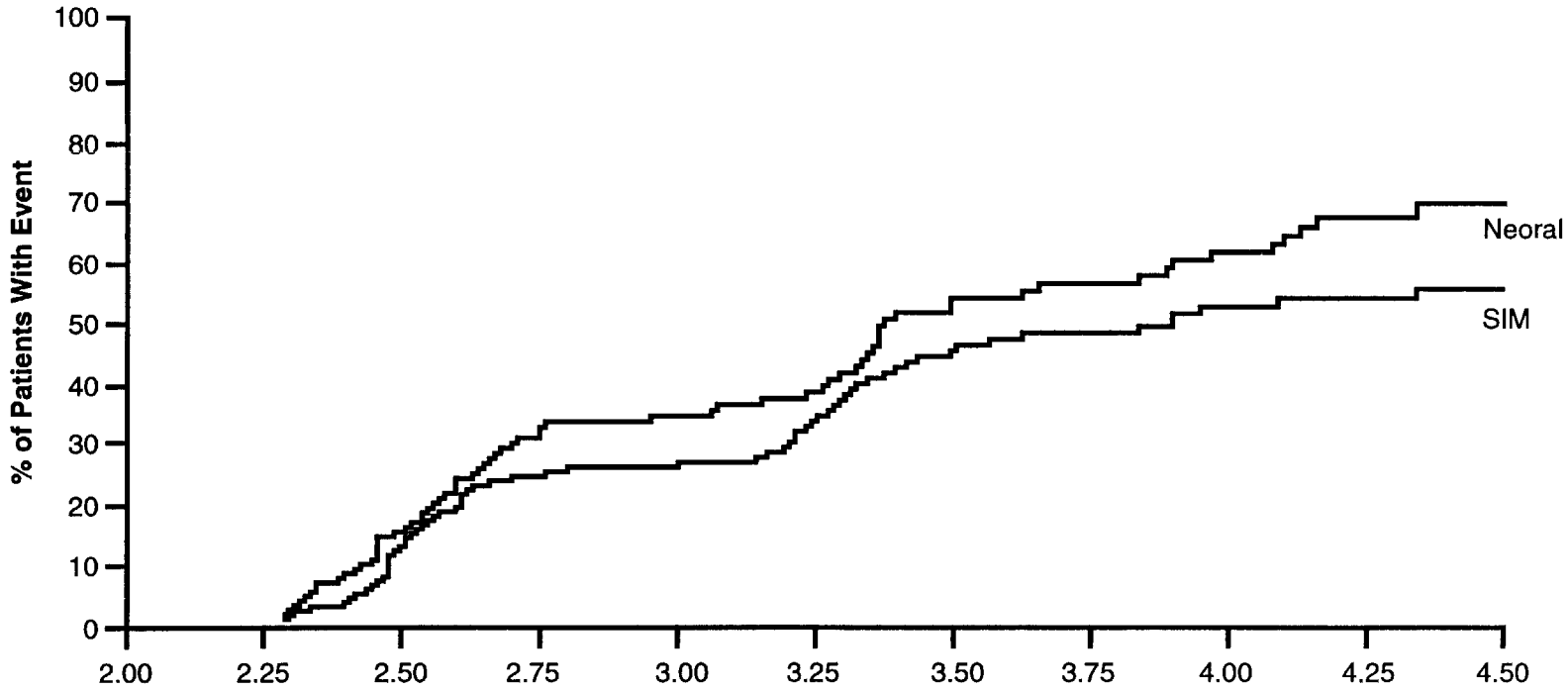
Study 652



*To be a responder, patient must also have completed the study.
†Values reported are for the randomized population.
‡Initial dosage.

CUMULATIVE INCIDENCE OF ACR RESPONSE BY MAXIMUM DAILY DOSAGE PRIOR TO EVENT

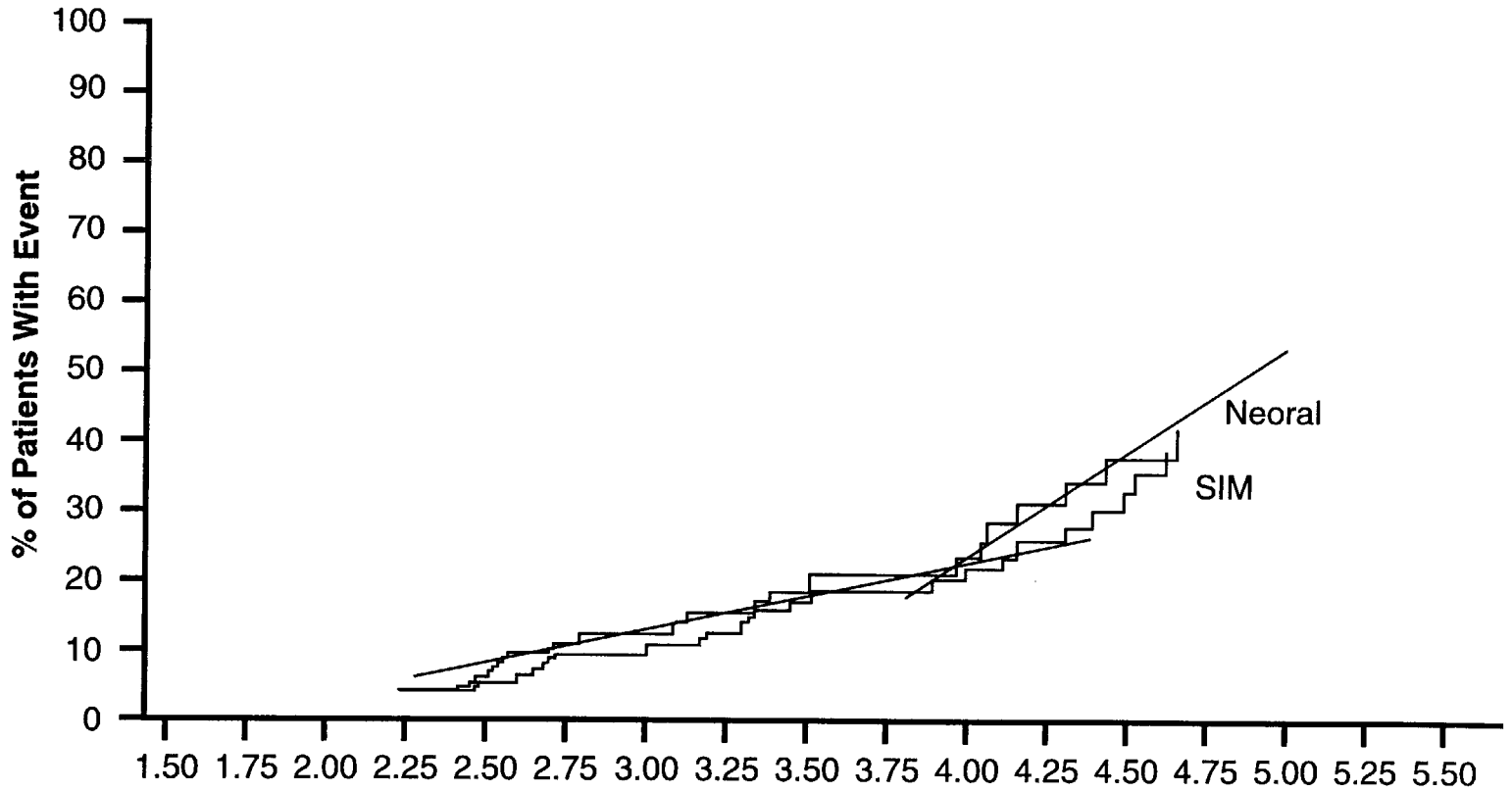
Study 302



Patients at Risk											
Neoral (n)	0	139	117	81	78	67	44	39	32	26	24
SIM (n)	147	146	130	101	97	81	63	52	48	41	33

PERCENTAGE OF PATIENTS WITH ≥50% INCREASE IN SERUM CREATININE BY MAXIMUM DAILY CsA DOSAGE PRIOR TO EVENT

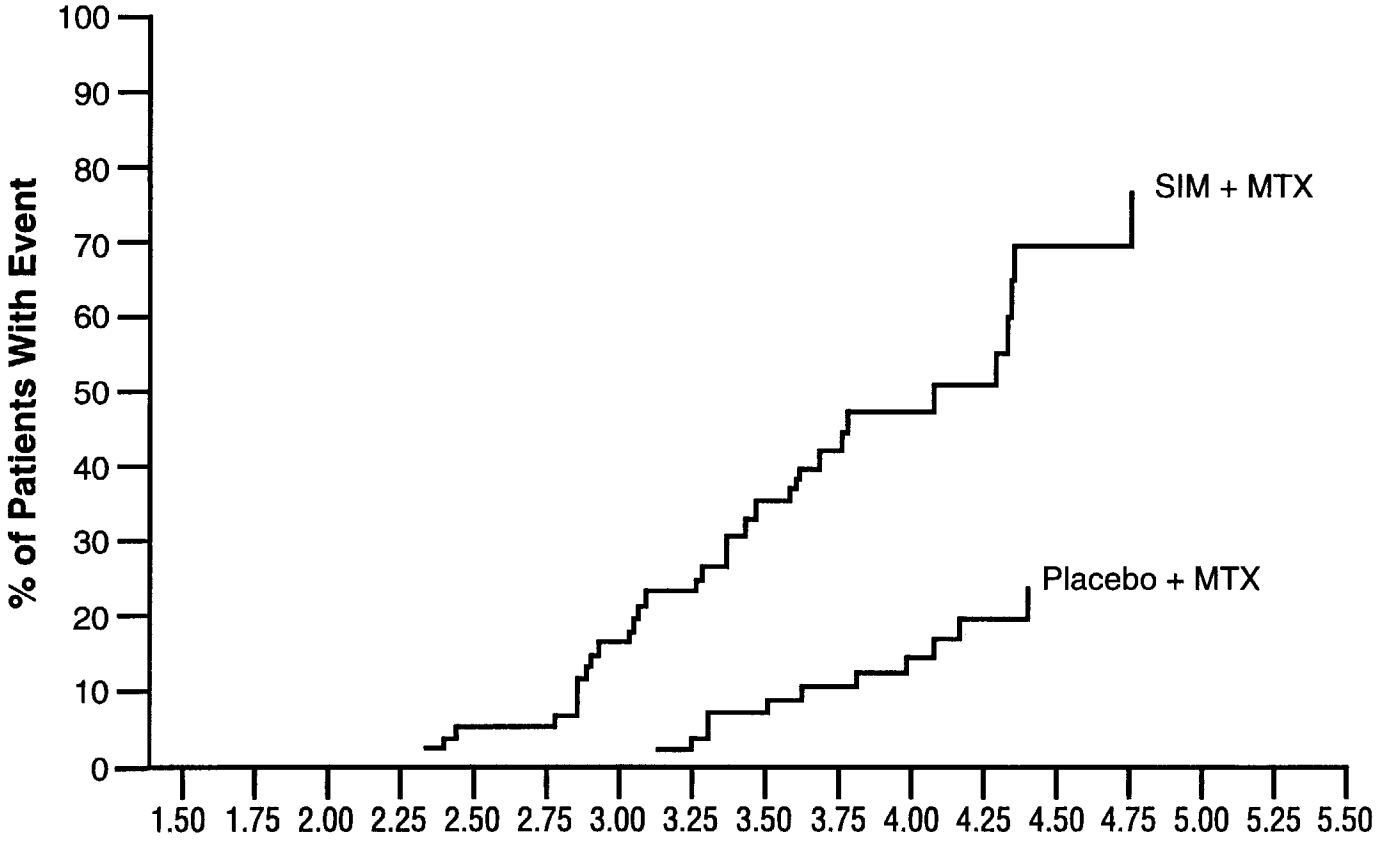
Study 302



Patients at Risk																
Neoral (n)	139	139	139	120	89	80	66	45	38	31	23	17	13	5	2	0
SIM (n)	147	147	145	133	111	108	85	66	57	50	37	28	17	15	5	1

CUMULATIVE INCIDENCE OF ACR RESPONSE BY MAXIMUM DAILY DOSAGE PRIOR TO EVENT

Study 654



Patients at Risk																
SIM + MTX (n)	69	69	69	64	60	49	42	30	21	15	11	6	2	2	2	2
Placebo + MTX (n)	71	71	71	70	67	66	63	55	50	37	25	15	9	3	1	0

CLINICAL PERSPECTIVE

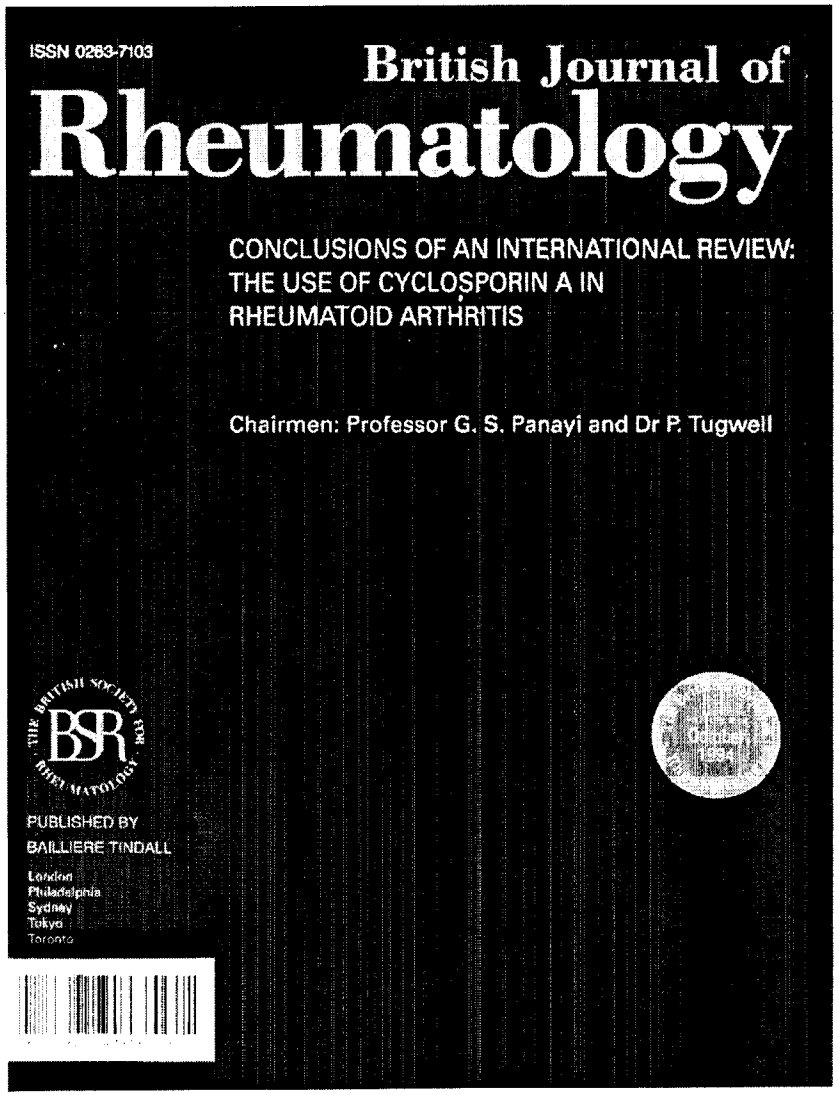
Peter Tugwell, M.D.

Chairman, Department of Medicine
University of Ottawa

A PERSONAL VIEW OF RISK/BENEFIT OF CsA IN RA PATIENTS

- This view is based on my experience with CsA
  - As a clinical rheumatologist who has used CsA for 15 years
  - As coprincipal investigator on two of the labeling studies—study 2008 (with Dr C. Bombardier) and study 654 (with Drs T. Pincus and D. Yocum)
  - As cochairman of three international consensus guideline conferences on the use of CsA in RA (with Prof G. S. Panayi)

INTERNATIONAL CONSENSUS GUIDELINES ON THE USE OF CsA IN RA PATIENTS



STATEMENT OF INDUSTRY SUPPORT FROM SANDOZ/NOVARTIS

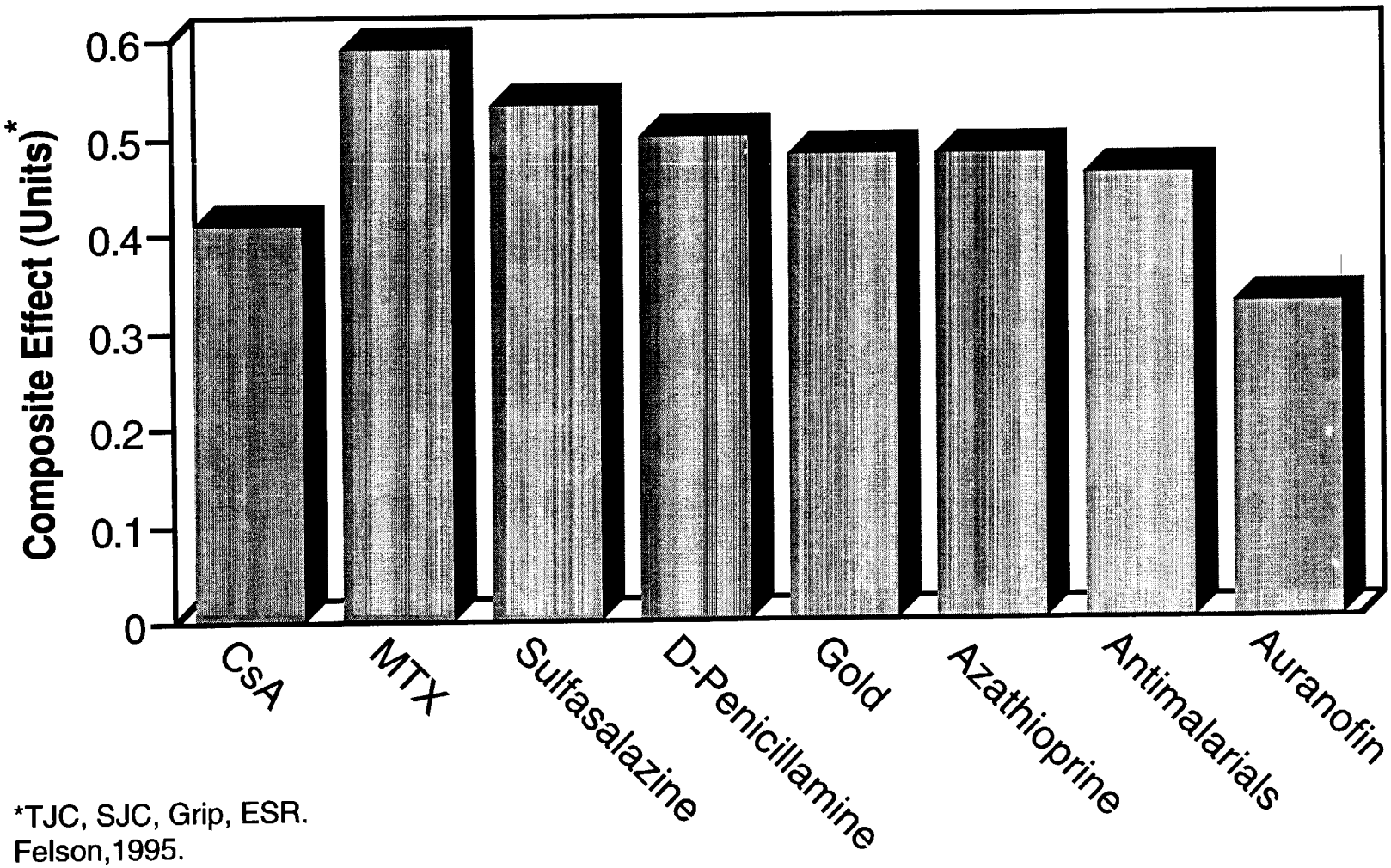
- Grants in aid for CsA studies
- Consultant/speaker at conferences
- Consultant in preparation of FDA submission

REVIEW OF BENEFIT/RISK

- **Efficacy comparable to other SAARDs**
- Tolerability similar to other SAARDs
- Can be used in combination with other SAARDs

COMPARISON OF CsA TO OTHER SAARDs IN RA PATIENTS

- **CsA has shown moderate efficacy**



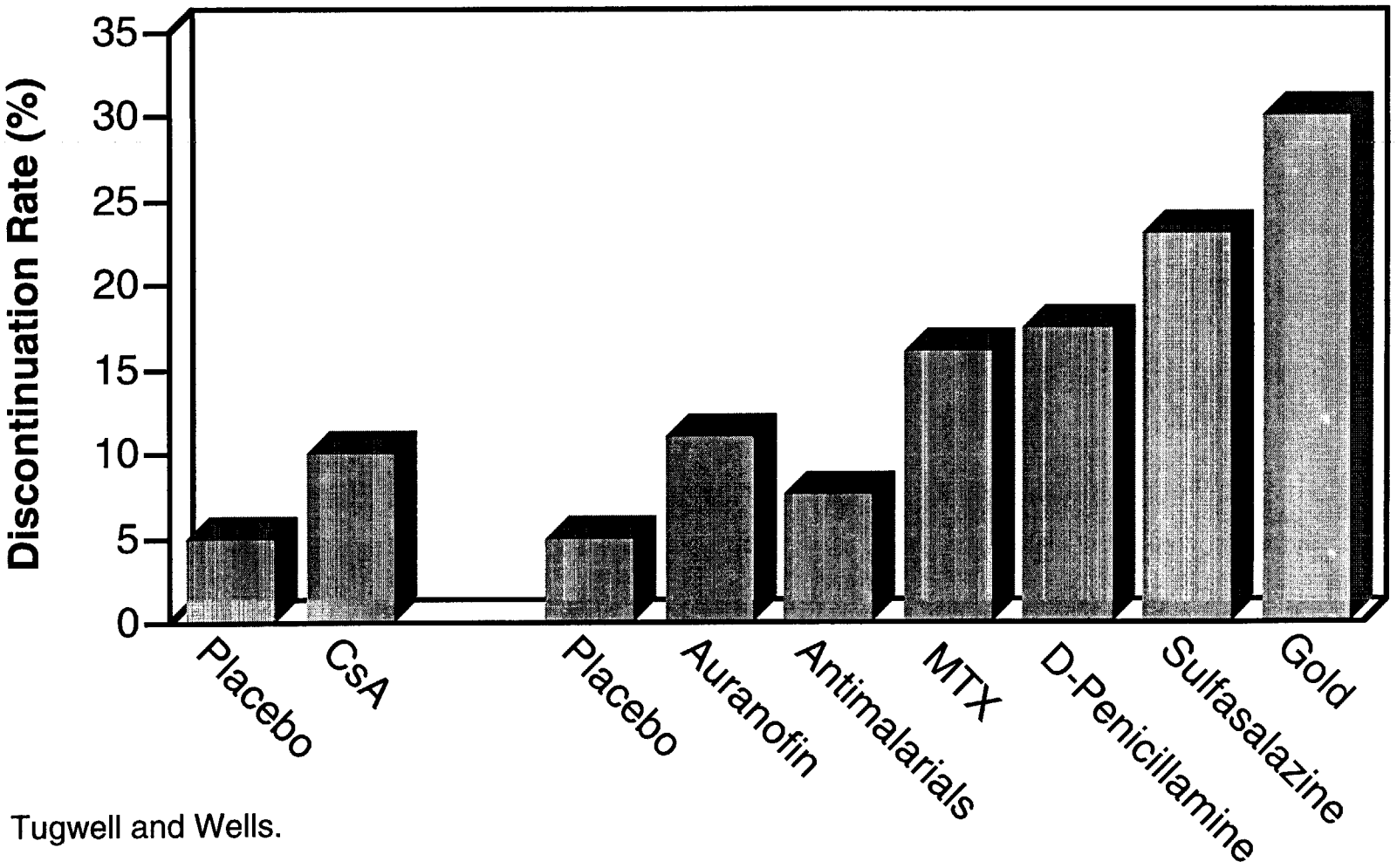
*TJC, SJC, Grip, ESR.
Felson,1995.

REVIEW OF BENEFIT/RISK

- Efficacy comparable to other SAARDs
- **Tolerability similar to other SAARDs**
- Can be used in combination with other SAARDs

COMPARISON OF CsA TO OTHER SAARDs IN RA PATIENTS (cont)

- **Numbers of CsA patients who discontinued because of toxicity are similar to those of patients treated with other SAARDs**



Tugwell and Wells.

REVIEW OF BENEFIT/RISK

- Efficacy comparable to other SAARDs
- Tolerability similar to other SAARDs
- **Can be used in combination with other SAARDs**

COMPARISON OF CsA TO OTHER SAARDs IN RA PATIENTS (cont)

- CsA can be used in combination with MTX
- There are also some data on CsA used in combination with hydroxychloroquine and gold

MANAGEMENT GUIDELINES FOR CsA THERAPY IN RA PATIENTS

- Educate patient to ensure patient understands importance of compliance with monitoring and avoidance of new medications without discussion with physician
- Start CsA at 2.5 mg/kg/day; give split dose bid
- Increase dosage to 3.0 mg/kg/day at 4 weeks and to 3.5 mg/kg/day at 8 weeks in absence of adverse events
- Decrease dosage by 25% if patient's serum creatinine is ≥30% of baseline
- Evaluate patient at 2-week intervals until maintenance dose is achieved and monthly thereafter—especially serum creatinine and blood pressure. Continue monitoring serum creatinine and blood pressure with physician review of the results for as long as patient takes the drug
- Extra monitoring in patients
  - 65 years of age and older
  - With preexisting hypertension
  - Using concomitant nephrotoxic agents or drugs that could raise CsA levels

SUMMARY

- CsA is not a "silver bullet" that puts RA patients in remission
- CsA is a SAARD with moderate efficacy that provides some patients with a clinically important benefit over placebo either as SAARD monotherapy or as SAARD combination therapy with MTX in patients with inadequate response to MTX
- Considerable experience not only in transplant patients but also in more than 20,000 RA patients worldwide provides reasonable database for risk/benefit
- Risks need to be taken seriously
- Risks can be managed by adherence to the international guidelines, which are emphasized in the proposed package insert
- In my experience, CsA is a useful product for the treatment of patients with severe RA

ISSUE 3 FOR THE COMMITTEE

What additional data, if any, would be needed in JRA to permit the labeling (via the "Pediatric Rule") for polyarticular JRA?

"PEDIATRIC RULE"

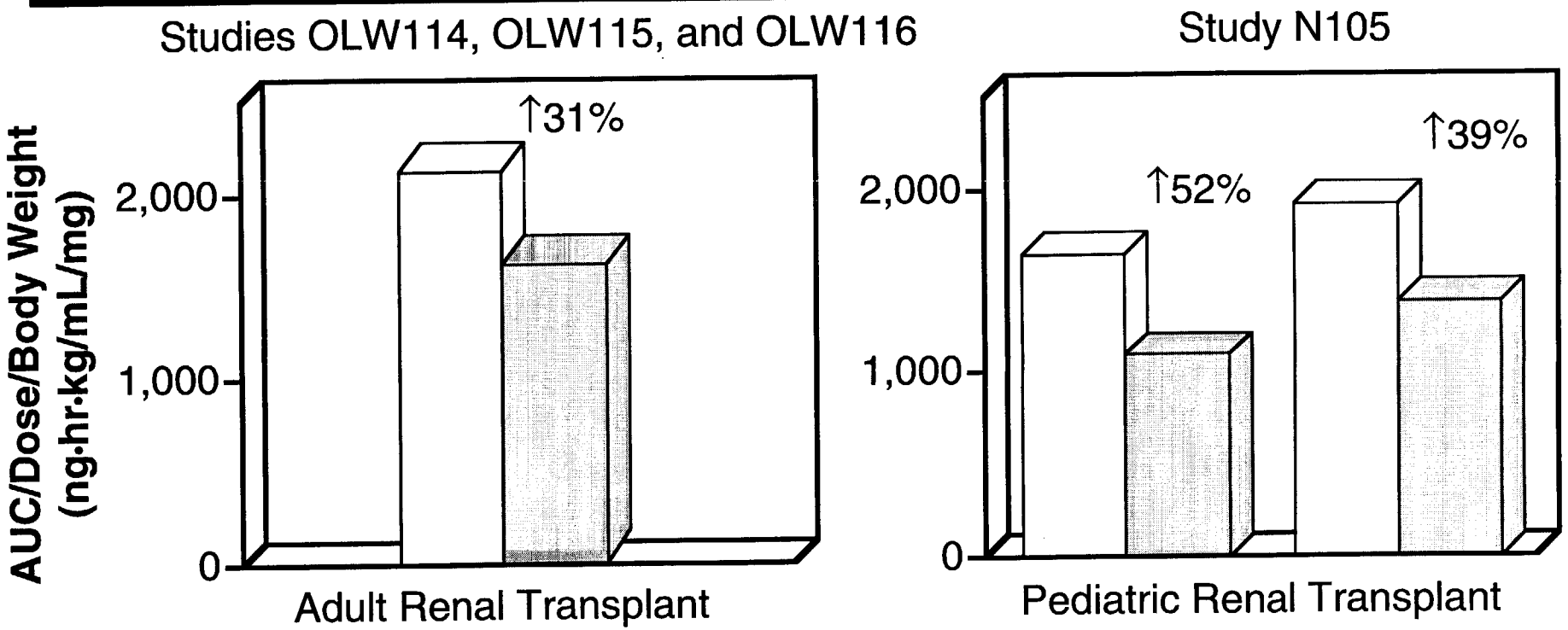
"For new agents not yet approved for adult RA, adult efficacy data can be used to support a signs and symptoms claim for polyarticular JRA if there is biologic plausibility that the agent would have a similar effect in JRA."

Vibeke Strand, MD

Biopharmaceutical Consultant
Clinical Associate Professor
Division of Immunology
Stanford School of Medicine

BIOAVAILABILITY OF NEORAL VS SIM

Comparison of Stable Renal Adult Transplant and Pediatric Transplant Patients



N	55	12	18
Mean Age (yr)	50.8	8.9	14.6
(Range)	25-66	4-11	12-18

Neoral SIM

CsA IN JRA
Conclusions

IN THE CONTEXT OF THE PEDIATRIC RULE:

Based on efficacy in adult RA, expected to be beneficial in RF+ polyarticular JRA

Reported series show benefit in refractory systemic JRA; as many as 50% develop polyarticular disease

The literature supports the biologic plausibility of the use of this agent in the treatment of polyarticular JRA

Arthritis Advisory Committee

Food and Drug Administration
Center for Drug Evaluation and Research

February 5, 1997

Gaithersburg Hilton
620 Perry Parkway, Gaithersburg, MD.

"Guidance for Industry in Designing Clinical Programs for Developing Drugs, Devices or Biological Products Intended for the Treatment of Rheumatoid Arthritis (RA)"

Contents

DRAFT

Agenda

Arthritis Advisory Committee
Food and Drug Administration
Center for Drug Evaluation and Research

February 5, 1997

Gaithersburg Hilton
620 Perry Parkway, Gaithersburg, MD.

"Guidance for Industry in Designing Clinical Programs for Developing Drugs, Devices or Biological Products Intended for the Treatment of Rheumatoid Arthritis (RA)"

8:00 Call to Order, Introductions: Michelle Petri, M.D., Chair
Meeting Statement: Kathleen Reedy, Executive Secretary
Welcoming Comments: Wiley A. Chambers, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

8:15 **Open Public Hearing**

8:45 **Introduction to the Document: Kent R. Johnson, M.D.**
Medical Officer, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

8:55 **DISCUSSION**

Adult Claims: major clinical response
use and definition
Quality of Life: duration of trials

10:35 **Break**

10:45 **DISCUSSION**

Statistical Considerations: Equivalency Standards
Dropout design addendum

11:45 **Lunch**

1:00 **Discussion**

JRA Claims and Questions
Eligibility of JRA patients for trials
Inclusion of Subsets and Inferences drawn
Phase 4 studies
Safety issues
Registries

5:00 Adjourn

GUIDANCE FOR INDUSTRY

CLINICAL DEVELOPMENT

PROGRAMS FOR DRUGS, DEVICES,

AND BIOLOGICAL PRODUCTS

FOR THE TREATMENT OF

RHEUMATOID ARTHRITIS (RA)

DRAFT GUIDANCE - NOT FOR IMPLEMENTATION

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U.S. Department of Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health

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GUIDANCE FOR INDUSTRY[1]

CLINICAL DEVELOPMENT

PROGRAMS FOR DRUGS, DEVICES,

AND BIOLOGICAL PRODUCTS

INTENDED FOR THE TREATMENT OF

RHEUMATOID ARTHRITIS

This document is intended to assist developers of drugs, biological products, or medical devices intended for the treatment of rheumatoid arthritis (RA) by providing guidance on the types of claims that could be considered for such products and the clinical evaluation programs that could support those claims. Section I addresses types of claims that are available for the treatment of RA and the measures used to support such claims. Section II contains guidance on the timing, design, and conduct of preclinical and clinical trials for RA products. Section III contains guidance specifically pertaining to biological products. Section IV contains guidance pertaining to devices, and Section V contains guidance on special considerations for juvenile RA.

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[1](When Finished) -- This guidance has been prepared by the Rheumatology Working Group of the Medical Policy Coordinating Committee (MPCC) of the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health. Although this guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the industry, it does represent the agency's current thinking on the evaluation of drugs, devices and biological products intended for the treatment of Rheumatoid Arthritis. For additional copies of this guidance contact the Division of Communications Management (formerly the Executive Secretariat Staff), HFD-210, Center for Drug Evaluation and Research, FDA, 5600 Fishers Lane, Rockville, MD 20857 (Phone: 301-594-1012). An electronic version of this guidance is also available via Internet using FTP, Gopher or the World Wide Web (WWW). For FTP, connect to the CDER anonymous FTP server at CDVS2.CDER.FDA.GOV and change to the "guidance" directory. For Gopher connect to the CDER Gopher server at GOPHER.CDER.FDA.GOV and select the "Industry Guidance" menu option. For WWW, connect to the FDA Home Page at WWW.FDA.GOV and go to the CDER section.

I. CLAIMS FOR THE TREATMENT OF RA

Over the past decade, there has been a search for better measures to describe patient outcomes in RA clinical trials. A number of organizations, including the International League Against Rheumatism, the American College of Rheumatology (ACR), and the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) group, have attempted to define core groups of measures as well as composite indices describing patient outcomes. As a result of these efforts, several new measures have been described and validated with clinical data. These outcome parameters are now being used in clinical trials during drug development. For this reason, and in the hope that these measures will provide more useful information about patient outcomes, FDA is providing guidance about the use of these new measures in clinical trials that will support label claims.

In addition, many novel agents are under study for the treatment of RA. There is a search for more effective therapeutics that will have a positive impact on the natural history of the disease. The following label claims allow for descriptions of treatment effects of greater benefit than partial mitigation of signs and symptoms.

Although label claims have diverse legal and regulatory ramifications, their central purpose is to inform prescribers and patients about the documented benefits of the product. Because RA is a chronic, symptomatic disease that can result in a variety of adverse outcomes with different chronology, severity, and overall patient impact, various outcomes can be the bases for claims. The claims discussed in this section represent the current views of Agency rheumatologists about achievable and clinically relevant overall outcomes. In addition to the traditional claim of improving signs and symptoms, five further claims are described: improvement in functional capacity/health related quality of life, major clinical response, complete clinical response, remission and prevention of structural damage. More than one claim can be pursued simultaneously. It is anticipated, however, that under most circumstances, any of the additional claims will be approved only if there is adequate evidence to support the signs and symptoms claim.

Given the chronicity of RA, the signs and symptoms claim should be based on trials of at least 3 months duration (trials of ~~biologic agents should be at least 6 months in duration~~). Claims of improved functional ability/quality of life should be based on trials of at least 6-12 months and all other claims should be demonstrated in trials of at least one year. Some agents, by their nature, need to be evaluated for more than 3 months before a conclusion of effectiveness can be drawn. For example, it is recommended that most efficacy trials for biological drug products be at least six months in duration to assure that the response is durable and not undermined by neutralizing antibodies or other immune regulatory effects. **[FDA is soliciting comments from the Advisory Committee members on trial duration. A number of commenters thought that 6 months is more appropriate for the signs and symptoms claim but there is lack of consensus on how long trials assessing improved QOL should last].**

Given the importance of joint structure in long-term RA management, all trials lasting a year or longer, even if an X-ray claim is not sought, should include a structural assessment (e.g., X-ray, MRI). Trials evaluating claims other than signs and symptoms data should be designed to show superiority, unless active control agents approved for that claim are available.

Claims can be submitted singly or together. Because the persuasiveness of trials showing a difference is, in general, much greater than that of equivalence trials, it is highly desirable for a claim to be convincingly demonstrated in at least one trial showing superiority of the test agent over placebo or active control.

In some instances, a claim of superiority over a specific comparator, rather than a straightforward efficacy claim, will be sought. For example, the desired claim could be for efficacy superior to a specific non-steroidal anti-inflammatory drug (NSAID) for the treatment of signs and symptoms of RA. Substantiation of any claim of superiority over a specific agent should have two adequate and well controlled trials showing superiority. These trials could also be the basis for demonstration of the product's efficacy.

A. Reduction in the Signs and Symptoms of RA

This claim defines symptomatic benefit, or benefit that includes improvement in signs of disease activity as well as symptoms. Ordinarily this claim is established by trials of at least 12 weeks duration (at least 6 months for biologicals). Unless there is a reason to weight symptoms at the last visit more than intermediary symptoms, an analysis which equally weights all time points is appropriate. Acceptable outcome measures that would support claim A include:

1. Validated composite endpoints or indices of signs and symptoms

   These composites can be used to define a categorical endpoint of patient success or failure. For example, the Paulus criteria or the ACR definition of improvement (20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining core set measures: patient and physician globals, pain, disability, and an acute phase reactant[1] [2]) could be used to assess if a patient responded or not.

   [Illustration: Success for each patient in a six month trial could be defined as meeting the criteria for improvement over baseline in at least four of six observations, and not dropping out because of toxicity.]

2. Well-accepted sets of signs/symptoms measures

For example, the four measures previously recommended in the CDER Guideline for the Clinical Evaluation of Anti-inflammatory and Anti-rheumatic Drugs (1988) [joint counts (pain/tenderness and swelling) and global assessments (physician and patient)] or the ACR core set, may be used as outcome measures. The criteria for success and the methods for statistical analysis should be prospectively defined and agreed upon. For example, in using joint counts and global assessments, ordinarily a statistically significant difference between the control and the treatment group in change from baseline in at least 3 of the 4 measures is used as the criterion for a successful trial.

[Question to Advisory Committee members: what if a sponsor proposed using only one sign or symptom, e.g., joint swelling or patient global assessment? What additional substantiation would be convincing? How many measures are needed to support a plausible claim of relief of signs and symptoms?]

For both the above measures, the 66, 48 or 28 joint count is acceptable.

B. Improvement in Functional Ability/health Related Quality-of-life

This claim should be supported by success in both a validated functional measure for RA and a validated health related quality-of-life measure (either an RA-specific measure or a generic measure shown sensitive to RA), e.g., the health related HAQ and the SF-36. Trials supporting this claim should be at least 6-12 month's duration. **[Question for Advisory Committee members: How long is appropriate?]** An analysis according equal weight to all time points is usually appropriate. Ordinarily, proposals for a functional ability/health-related QOL claim should be for agents that have been shown to also improve signs and symptoms, either in the same or in other trials.

C. Prevention of Structural Damage

Prevention of structural damage is an important goal of RA therapy. Trials evaluating this claim should be at least one year in duration.

The following are examples of outcome measures that could be used to support prevention of structural damage claims.

D missing
p.5

E. Remission

The claim of remission defines substantial therapeutic activity with greater benefit to the patient than the mitigation of signs and symptoms of RA. Remission is defined as "remission by ACR criteria" and radiographic arrest (no change by Larsen or modified Sharp methods) over a continuous 6-month period while off therapy. Remission is not intended to imply cure. Trials intending to evaluate remission should be at least one year in duration.

F. Major Clinical Response

This claim is intended to define a substantial response in patients whose disease cannot remit by the above definition due to existing fixed deformities. The major clinical response claim is defined as a continuous 6-month period of (1) success by a yet to be determined criterion **[Issue for Advisory Committee members: There are several proposals for this. One is an algorithm of the ACR core-set (joint counts, globals, pain, function, and acute phase reactant) defined to "capture" only the best 10% of RA patient database used to derive the ACR 20% measure. An alternative proposal is to allow a prespecified number of joints to be invaluable up front, which would allow merging this category with D and E above. The algorithm will be discussed further at the meeting.]** and (2) radiographic arrest as defined above. This claim is based on statistically significant improvement in response rates above background therapy and, as with the claims of complete clinical response/remission, the trials would be at least one year's duration.

II. CONSIDERATIONS IN RA PRODUCT DEVELOPMENT

The following information on preclinical and early clinical development pertains primarily to pharmaceuticals (drugs and biologicals). The general principles outlined in sections C through F are applicable to devices; however, for information specific to the development of medical devices refer to Section IV in this document. Developers of products that combine therapeutic modalities (e.g., biologics and devices) may request assistance from FDA in designating a lead Center for review of the product. Such requests should be submitted to: Office of the Chief Mediator and Ombudsman (HF-7), Food and Drug Administration, 14-105 Parklawn Building, 5600 Fishers Lane, Rockville, MD 20857-001.

Frequently encountered issues in RA product development include:

(1) Selecting appropriate *in vitro* (animal or human systems) and *in vivo* animal models for screening potentially active agents;

(2) Designing and performing appropriate preclinical safety studies to support the use of a new molecular entity in human volunteers or patients;

(3) Balancing the potential need for therapeutic intervention early in the disease course with the need to avoid exposing patients with mild disease to agents that have toxicities or little record of safety;

(4) Identifying the potential risks associated with combination therapies, particularly those with shared target organ toxicity or potential for pharmacokinetic interactions;

(5) Designing adequate and practical long-term safety monitoring;

(6) Designing trials which definitively show clinical efficacy.

The following sections discuss approaches the above issues.

A. Preclinical Considerations

This section focuses on preclinical issues that are specific to the clinical development of anti-rheumatic therapies. In designing toxicity studies, and the timing of such studies, consultation with the agency is recommended concerning the current recommendations and guidelines that address drugs, devices and biological products. Guidance on preclinical safety testing, addressing the need for and design of toxicokinetic, reproductive toxicity, genotoxicity, and carcinogenicity studies, has been developed by the International Conference on the Harmonization of Technical Requirements for Pharmaceuticals (ICH). These documents are available via the FDA internet home page (http://www.fda.gov/cder or cber). Because biologics can pose unique challenges in animal study design (for example, species-specific binding or immunogenicity of human proteins in animals), there is a specific ICH document under development concerning the safety evaluation of biotechnology-derived pharmaceuticals ("Preclinical Testing of Biotechnology-Derived Pharmaceuticals").

1. Pharmacokinetics

Animal studies of drug absorption, distribution, metabolism and excretion are important during the early IND phase to aid in toxicity study interpretation but need not all be completed prior to Phase 1. Generally, for initial studies in humans, determination of pharmacokinetic (PK) parameters such as area under the curve (AUC), maximum concentration (C_{max}) and half-life ($t_{1/2}$) in animals is sufficient to provide a basis for predicting safe clinical exposure.

Preclinical testing of combinations of drugs (or biologics) to be used in patients with RA is often not feasible before the initial clinical trials since a variety of drugs , including NSAIDs, analgesics, corticosteroids, and disease modifying anti-rheumatic drugs (DMARDs) are currently used to treat RA patients. To evaluate potential interactions, information on the impact of concomitant therapies on pharmacokinetics may be needed to optimize dosing regimens and to identify potential safety concerns. Metabolic interactions often may be assessed in an *in vitro* system using animal or human liver slices, microsomal preparations, or purified p450 enzymes.

Interactions may also result from the presence of individual- or disease-specific factors, such as rheumatoid factor, which may bind to various monoclonal antibody therapeutics; *in vitro* binding studies which identify patients with high titers may be useful in identifying patients who may exhibit unique pharmacokinetics or patterns of clinical response.

2. Biological activity

The biological activity of a potential anti-rheumatic therapy should be established using multiple preclinical model systems (i.e., *in vitro, in vivo, ex vivo*). *In vitro* screens can utilize cells or tissues derived from animal or human sources and are generally used to select drug candidates that have a desired effect on a molecular target. Such assays can also be used to devise appropriate bioassays for the selected agent. Animals, either healthy, with rheumatic disease (spontaneous or induced) or genetically modified, are subsequently used to determine whether the biological effect can be demonstrated *in vivo*. While the *in vivo* system used should mimic one or more aspects of rheumatoid arthritis or its etiology, it is expected that each animal model will have its limitations.

a. *In vitro:*

Data from *in vitro* studies can be useful in defining the potential mechanism of a drug or biologic and for determining relevance of a particular animal species for *in vivo* assessment of activity or safety. These data are especially useful if a potential surrogate marker can be identified in preclinical studies. For example, if the product is intended to affect the CD_4 receptor on lymphocytes, this receptor may be used as a surrogate marker for both activity and certain toxicities.

Several *in vitro* tests may be utilized depending on the mechanism of action of the drug or biologic. For example, binding assays may be useful for developing receptor antagonists or monoclonal antibodies. *In vitro* functional assays, e.g., platelet and neutrophil aggregation, may be useful tests for identifying inhibitors of inflammatory mediators. Enzymatic assays (such as *in vitro* or *ex vivo* inhibition of cyclooxygenase, lipoxygenase and phospholipase) may also be useful for determining selectivity for the inhibition of isozymes.

b. *In vivo*

Selection of animal models should be made on the basis of pharmacodynamic responses, similarity of animal disease etiology to clinical disease, and/or to define mechanism-based toxicity. Ideally, products that are targeted for a subset of arthritic patients should be developed in an experimental model(s) that is most relevant to that subset. For example, rats are not sensitive to drugs which inhibit 5-lipoxygenase. Therefore, mouse or rabbit models are more relevant to evaluate the anti-inflammatory activity of leukotriene inhibitors.

The development of rheumatic disease models to allow screening for potential RA drug candidates is encouraged. The following examples are meant only to illustrate some models which are in current use and are not intended to suggest excluding the use of others.

Collagen-induced arthritis (CIA)

Collagen-inducted arthritis is often considered to be a suitable model for studying potential drugs or biologics active in human rheumatoid arthritis because of the involvement of localized major histocompatibility complete class II-restricted T helper cell activation and similar histopathological lesions. Radiographs of joints affected by CIA often show erosive changes similar to those seen in human rheumatoid arthritis. The progressive arthritis often results in RA-like joint deformity and dysfunction. Anti-collagen antibodies, which occur in some patients with RA, develop in the CIA model.

The collagen-induced arthritis model has been useful for identifying immunosuppressants and steroid hormones as well as inhibitors of inflammatory mediators. Since this model can be induced in several animal species it may be especially useful for evaluating drugs that have species-specificity, e.g., leukotriene antagonists and 5-lipoxygenase inhibitors. In addition, while functional tests are not routinely used in

this model, incorporation of measures of mobility and joint function may enhance its predictive value.

Naturally occurring arthritis or autoimmune response:

MRL/lpr mice, Biozzi H mice and DBA/1 mice have been used to examine the onset of drug-induced tolerance and immunosuppressant drug effects on autoimmunity. The MRL/lpr mouse model has been useful for evaluating immunosuppressants and hormones.

Rat carrageenin-induced acute model of inflammation:

This model has been useful in assessing anti-inflammatory activity of cyclooxygenase inhibitors. Most of the animal models that involve inflammation in the paw may be used for measuring antiphlogistic action of a drug.

Adjuvant-induced arthritis in rats (AA):

AA in rats has been frequently used for screening non-steroidal anti-inflammatory drugs and inhibitors of inflammatory cytokines as well as antimetabolite-like immunosuppressants.

Streptococcal cell wall-induced arthritis:

This model has been used for developing cytokine inhibitors.

Experimental organ transplant in animals:

This model has been used to identify the activity of immunosuppressants and antimetabolites, particularly those directed at cytolytic cellular immune processes.

Transgenic animal models:

A number of transgenic animal models are being developed for the study of rheumatoid arthritis and may prove useful over the next decade. Some examples include: transgenic mice that carry genes for the env-Px region of the human T cell leukemia virus type I genome, humanTNF, CD4, HLA B-27 etc.

3. Toxicology

Preclinical toxicology studies of a drug or biological product are designed to characterize general and specific toxicity using dosing routes and regimens as similar as possible to the proposed clinical trials with consideration of the demographics and disease status of the intended patient population. For instance, the prevalence of RA is high in females. Therefore, reproductive toxicity studies should be completed early in clinical development to support the inclusion of women of child bearing age in early phases of clinical trials.

Immunomodulatory or immunosuppressive agents administered to RA patients as monotherapy or in combination raise concerns about the adverse effects of prolonged immunosuppression. For example, malignancies (i.e., lymphomas) are a known risk of long- term, non-selective immunosuppression used for treatment of graft recipients. Investigational drug-related opportunistic infections and mortality related to immunosuppression have occurred in RA patients. Sponsors are encouraged to identify and utilize animal models which may assist in selecting drug candidates that selectively inhibit cells and processes responsible for RA.

Anti-rheumatic drugs are often used in combination in an attempt to improve outcomes and minimize toxicities. However, drug interactions may result in increased toxicity, even at lower than previously evaluated doses of either agent. This concern is especially evident for agents which have long half-lives or non-selective activity, or for drugs which share common target organ toxicity. Preclinical toxicity studies which evaluate the use of combined agents may be helpful in predicting clinical safety hazards. The duration of toxicity dosing of animals is usually linked to patient dosing regimens. Development and validation of *in vitro or* whole animal models is encouraged to address concerns regarding short or long-term patient risk due to immunosuppression.

B. Pharmacokinetic/Pharmacodynamic Strategies

FDA is currently developing specific guidance for the performance of studies to characterize the PK/PD performance of products which should be consulted when it is completed (expected completion 6/97). *In vivo* pharmacokinetic studies are needed to evaluate drug disposition and metabolism, degree of linearity and accumulation, dose proportionality, and, for oral dosage forms, food interactions.[4] Some of these data may be gathered in a single study

designed to evaluate a number of parameters. During formulation development, bioequivalence studies linking formulations may be necessary.

Because polypharmacy is common during the treatment of rheumatic disorders, *in vitro* binding studies with blood from patients with active disease should be used as a preliminary screening tool for potential displacement reactions.

For products that may interact with rheumatoid factors, e.g., monoclonal antibodies, the frequency of patients with RF reactive to the antibody, as well as the impact of interactions on the pharmacokinetics of the product, should be evaluated when possible.

C. Considerations in Phase 1 Trials

For general information on clinical development pertaining to most drugs and biological products, see "General Considerations for the Clinical Evaluation of Drugs."[5]

"Phase 1" has two connotations: one refers to the earliest, first-time-into-humans trials, while the other encompasses studies of pharmacokinetics, metabolism, drug interactions, special populations and other clinical pharmacology trials described above. It is expected that both kinds of Phase 1 trials will ordinarily be conducted during the clinical evaluation of therapies for RA. This section is primarily intended to discuss issues related to the first time people are exposed to the drug (including to a particular dose level, or duration of therapy).

1. Settings and investigators

First-time-into-humans Phase 1 studies should be carried out in institutions with a full range of clinical and laboratory facilities and the patients should be kept under close observation. It is desirable that the trials be under the direction of physicians with experience in early drug development and rheumatology, or that a team of investigators combining experience in rheumatology and clinical pharmacology be employed.

2. Subjects

First-time-in-humans drug trials are frequently conducted in healthy volunteers. Such studies are predicated upon the ability to perform, and to interpret the results of, preclinical animal tests. If the preclinical testing does not reveal potential mutagenic, immune system or

potentially serious effects at or near the expected therapeutic range, testing in volunteers is initiated However, for biological and drug products that have potentially serious toxicities, it may be appropriate for initial testing to be performed in patients with some potential to benefit. This has created challenges in selecting an appropriate initial patient population.

For drugs and biologics that have been tested in relevant preclinical toxicity evaluations and have been found relatively safe, without the potential for mutagenic, immune system or other serious effects at the proposed doses, trials may be initiated in healthy volunteers. If however, significant effects have been demonstrated or might be possible, selection of an appropriate patient population is necessary. It is recommended that patients meet the ACR criteria for both diagnosis and activity of RA and be without other serious medical conditions. Patients with minimal disease are sometimes not appropriate for the same reasons that the testing is not initiated in healthy volunteers. Patients with devastating RA may also not be the best starting population because of the medical complications of their disease. In addition, they may be less likely to respond to therapy.

There is ongoing epidemiologic work on identifying markers of increased risk in RA: these could be useful for identifying patients with poor prognoses who might be considered for very aggressive treatments (e.g., immunoablative therapies followed by stem cell transplants) of potential high toxicity. Application of epidemiologic studies may allow a very aggressive treatment to be restricted to a subset of RA patients who have a demonstrated shortened lifespan due to their disease, e.g., subjects with greater than 30 affected joints or a score on the HAQ with fewer than 75% of questions answered "with ease."

In any case it is particularly important that informed consent be complete and that some provisions be made to assess that patients understand what they are consenting to. If the potential exists for disease exacerbation, this should be part of the informed consent.

When the characteristics of the agent suggest that it may potentially have long-term gonadal effects, it is desirable that men and women not wishing to parent children be chosen for Phase 1 studies.

3. Trial design

Ordinarily, initial Phase 1 studies are sequential dose escalation trials, in which safety and tolerance at a specific dose is established before exposing additional subjects to a higher dose. A single dose is almost always tested first, followed by repeated dose studies; however, this design is influenced by the type of agent used. Although escalating the dosage to a clearly determined maximum-tolerated-dose (MTD) will aid future trial design, in some instances it is not medically prudent to try to fully characterize the MTD. Additionally, for some products, an MTD may not be definable.

The starting drug dose chosen is often a "no adverse effect" dose (determined by interspecies mg/m^2/day dose conversion from animal to human). For biologicals, the initial dose chosen is often one thought to have no adverse biologic effect. Conservative dose escalations (e.g., half log or less), are usually recommended.

4. Concomitant therapy

Use of low-dose corticosteroids (up to 10 mg prednisone equivalent daily), and NSAIDS may ordinarily be continued in Phase 1 trials. Concomitant therapy with methotrexate and similar agents should be avoided in initial phase 1 trials of all novel antirheumatic drugs, biologics and devices because of the difficulty of differentiating the toxicity of the novel agent from that of the co-administered product.

Physicians now prescribe methotrexate and similar agents earlier in the course of rheumatoid arthritis. Recruiting adequate numbers of patients not taking these agents may be difficult. Approaches which may allow the use of methotrexate and similar agents in later Phase 1 trials include: (a) obtaining reassuring evidence of lack of toxicity from relevant animal models in which co-administration occurred; and (b) starting at doses significantly lower than the "no adverse effect level" of the single agent as determined by preclinical studies. Such proposals should be discussed in the planning stages with Agency staff.

5. Observations

a. Safety

The standard batteries of safety observations have been described elsewhere. However, additional types of safety observations may be necessary, e.g., tests of effects on cellular and humoral immune function or host defenses. For products with the

potential for effects lasting long after administration, or for delayed toxicity, appropriate follow-up should be designed. For example, Phase 1 studies of agents used to deplete or modify the function of T-cell subsets should be designed to carefully assess both the short and long-term effects on number and functional status (e.g., DTH responses) of cell populations and other pertinent pharmacodynamic assays during therapy and during follow-up.

It is desirable to incorporate individual patient adverse event stopping/withdrawal "rules" into protocol designs. In addition, incorporation of stopping or modification rules for adverse events into trial designs is often advisable. For example, dose escalation rules should be clearly defined in dose-finding studies, with provisions for enrollment of additional patients at a given dose if possible significant adverse events are observed at that dose.

b. Efficacy

Developing an understanding of the agent's therapeutic potential in early trials is highly desirable for efficient product development. This may be attempted in Phase 1, but can only be achieved by performing controlled trials. RA responses in open trials are of questionable value in indicating efficacy. Consideration should be given to the more modest goal of determining whether the pharmacological effect predicted from the preclinical development is present (proof-of-concept).

D. Considerations in Phase 2 trials

During Phase 2, larger, often longer-term trials are employed to better define the dose- and exposure-related activity and toxicity of the agent. Enough information should be generated to ensure that the Phase 3 trials can be conducted safely and with a high probability of success. In addition, Phase 2 trials should solidify a total drug development strategy, to ensure that, after the Phase 3 safety/efficacy trials are done, all of the information needed for registration will have been gathered, including an appropriate safety database, clinical pharmacology, dose response data, the exploration in special populations (e.g., renal failure, hepatic failure), and drug interaction information with agents expected to be co-administered.

There is nothing to preclude conducting additional "Phase 1" clinical pharmacology studies and Phase 2 trials while the Phase 3 development is ongoing.

The following issues are important for Phase 2 trials in RA:

1. Dose finding

This is a central challenge of Phase 2 development. Once a reasonably safe range of doses has been established, randomized, parallel arm dose-comparison trials are ordinarily recommended. The use of a placebo arm is desirable for several reasons. First, if no difference is found among doses, there is usually no other way to determine whether all doses were equally effective or equally ineffective. Second, if a dose-response trend is found, the placebo arm may indicate the possible magnitude of the observed effect. If use of a placebo is not possible, designs should include wide dose ranges (durations, repetitions, etc.). Active-controlled designs that specify an arm with a well-characterized, known therapy can also be very useful.

Signs and symptoms measures may be used for dose finding studies, i.e., it is not contemplated that separate dose-finding be done for the longer-term endpoints.

For agents that are thought to have prompt action and rapid offset of effect, alternative designs, including cross-overs and titration designs, may be useful, although historically this has not been the case. Trials of two or more doses which permit liberal titrating per the patients' responses are unlikely to clearly demonstrate a dose response, because these titration designs result in a blurring of any real dose distinction that may exist.

The desirability of identifying a range of doses with acceptable toxicity and reasonable activity, for study in Phase 3, cannot be stressed enough.

2. Safety

Every RA investigational therapy raises safety concerns. Whenever there is a potential for significant, long-lasting or delayed-onset toxicities, it is desirable to design the Phase 2 studies to provide a group of patients with longer-term follow-up preceding the larger Phase 3 studies. Provisions for long-term follow-up can be helpful in addressing issues prior to approval/registration (e.g., issues relating to the potential

for immunosuppression, opportunistic infections, neoplasia, and induction of autoimmune disease).

It is desirable to develop a standardized toxicity grading scale for use in all trials of a product, based on the known and suspected toxicities of the product, or of the drug class. This scale may be developed in early Phase 2. This may improve consistency of adverse event reporting, and allow more accurate comparisons among trials.

3. Additional development aspects

a. Concomitant therapy

Before starting Phase 3 trials, an evaluation of the test product's interaction with the other agents likely to be used by the target population should be performed. Initial information can be established based on metabolic pathways, studies of in vitro systems, animal or human pharmacology studies, or drug interaction studies. This type of information is helpful in directing areas in need of clinical evaluation. When products are intended to be tested as combination therapy with the investigational agent, substantial information on interactions and safety of co-administration should be developed in Phase 2.

b. Gender effects

Most RA trials have predominantly female enrollment. Sponsors should evaluate whether the observed safety and efficacy findings are restricted to women or can be also extrapolated to male subjects. This may be accomplished by subset analyses from trials, PK data, or other information.[6]

E. Efficacy Trial Considerations

The overall goal of Phase 3 work is to demonstrate the efficacy of the product in convincing controlled trials, and to accrue a sufficient safety database. Efficacy trial protocols should contain an analytical plan that precisely identifies the primary comparison(s) to be made, the criteria for success of the trial, and the statistical tests that will be used. These should be linked to the labeling claim that would be supported by the trial. Any additional planned, ongoing, or completed trials that are also intended to support the claim should be identified.

1. Global considerations

a. Patient selection

1) Activity of disease: Unless some other specific subgroup is targeted, patients enrolled in efficacy trials should at a minimum have disease definition and disease activity as defined by ACR criteria. Consultation with the Agency on the generalizability of claims derived from trials with significant limitations on entry criteria is recommended.

To enhance the power of the trial, strategies to improve the chances of a response to therapy are often employed. Some designs incorporate an attempt to select active patients by withdrawing background treatment and allowing patients to "flare". Only individuals with sufficiently high scores are enrolled. The relevance of this type of observed flare is questionable and its ability to predict active disease has not been established. Many patients randomized to placebo in such studies exhibit the characteristic response of rapidly returning almost to baseline without further treatment. In addition, when patients undergo blinded withdrawal from therapy within these trials, similar dramatic flares are not observed. This raises the question of whether there is an expectation bias on the part of patients, who have been told about the flare procedure, and ascertainment bias on the part of investigators, who wish to have patients meet the entry criteria and enroll in the study. These uncertainties and instabilities around the outcome measures used in such trials should be kept in mind when employing these designs.

A proportionately smaller, but nevertheless noticeable and prompt "regression to the mean" is noted in the joint scores of patients required to have a certain minimum value for trial entry in trials not employing a "flare" strategy. This means that patients, on the whole, will not actually be as active as anticipated when the entry criteria are set. The mechanisms are similar to the above example.

2) Subgrouping patients by disease markers: RA is likely composed of a number of more or less distinct diseases delineated by a common genetic background,

corresponding clinical manifestations, similar serologies, and responses to therapy and prognoses. The study of RA may be enhanced by using more homogeneous groups defined by markers with clear prognostic significance. Novel epidemiologic and molecular genetic approaches may lead to identification of even more subgroups. However, prospective studies are first needed to confirm the clinical usefulness of new purported prognostic factors. Where existing data do support markers as prognostic indicators (risk factors), the presence of rheumatoid factor, erosive or vasculitic disease, and DR4 homozygosity, should be taken into consideration in the design of trials. Although in some cases such studies may limit generalizability and impact labeling of the final product it is also possible that such targeting may improve the risk/benefit profile.

b. Concomitant antirheumatic therapy

Studies in RA patients, except in those with very mild disease, are carried out in the presence of concurrent active therapies, including steroids, NSAIDS, hydroxy chloroquine, etc. This concurrent therapy creates numerous challenges in patient selection, toxicity monitoring and clinical trial design. For example, since methotrexate therapy is used to treat many RA patients, new agents will be used in combination with methotrexate in clinical practice, unless a contraindication exists. Therefore, unless a prohibition on concurrent methotrexate is supportable, data regarding use of the investigational agent in combination with methotrexate is necessary to evaluate the potential for immunosuppression from combination therapy. Other agents may need to be similarly evaluated.

In addition, patients can be categorized according to their responses to standard therapy. Varying trial designs may be required to assess the response of different subgroups to an investigational therapy. For example, with respect to methotrexate use, the RA population can be divided into five groups: (1) methotrexate non-candidates - disease too mild or too early for methotrexate; (2) methotrexate candidates - disease sufficiently (or will become sufficiently) active to justify methotrexate; (3) methotrexate successes - disease reduced to negligible amounts; (4) methotrexate failures - clear drug failures,

for inefficacy or tolerability, and (5) methotrexate "partial responders" - with considerable residual disease despite methotrexate. Each of these groups might be considered separately for candidacy for an investigational agent, and with respect to an appropriate trial design. If only a subpopulation of RA patients (e.g. methotrexate non-responders) is studied in a particular trial, the results would ordinarily reflect efficacy only in that group. Any planned subpopulations should be clinically distinguishable. Sponsors should consult Agency personnel when planning a clinical development program contemplating an RA claim that is limited to a subpopulation of the disease.

c. Other Concomitant Therapies

Most patients with RA are taking concomitant medications. Use of medicines unlikely to influence treatment outcomes (e.g., antihypertensives) should simply be recorded, although investigators should be alert for possible drug interactions. The following approaches may be considered in dealing with arthritis medications or analgesics. Obtaining information during clinical development on co-administration of the test medication and expected concomitant medications is desirable.

1) Prohibit their use. This strategy may result in noncompliance or an increased number of dropouts.

2) Incorporate protocol-specified use, with monitoring. With this strategy, additional analgesic use (and possible other arthritis medications) may be used according to protocol specified criteria. In addition, for long duration studies, protocols should address whether intra-articular steroids are permitted and, if so, for how long assessments of the involved joint are excluded from analysis, and the manner in which "stress" doses of corticosteroids for surgery, etc., are to be handled and how soon after such doses protocol assessments would be allowed.

3) Design analgesic use, or its quantitative consumption, as (part of) an efficacy endpoint.

4) Define use of more arthritis treatments as (part of) an efficacy endpoint, or as (part of) a definition of treatment failure.

d. Stratification

Randomization is intended to balance confounders; however, in any specific trial, especially a small one, randomization may fail to achieve balance. It may be advisable to stratify known (or highly suspected) major risk factors to ensure their balance across arms. Any factor whose influence on the outcome is suspected to be as strong as the treatment's influence should be considered for stratification (e.g., erosive disease, presence of rheumatoid factor). An often overlooked risk factor is the patient's past therapeutic history. (See statistical section for further discussion)

e. Blinding

Because most RA outcome measures have a high degree of subjectivity, full patient and assessor blinding are usually needed for a credible inference. Designs may have compromised blinding if there is not an approximate parallelism in time to onset, nature of response, and toxicity profile. Trials should have parallel dosing in both arms so that a drug requiring frequent dose manipulations does not threaten the blind. If "arm specific" treatment adjustments are necessary, e.g., per monitored drug levels, these can be done by an unblinded (and sequestered) third party, in order to maintain patient and assessor blinding. Similarly, if the blind is likely to be compromised by infusion related events or other features of the treatment protocol, critical treatment endpoints such as joint counts should be assessed by an independent party with no knowledge of the subject's history.

f. Effects of dropouts and noncompliance.

It is important that trials be designed to minimize dropouts and the attendant information loss. Traditionally, recommended RA trial designs have focused on eliminating sources of variability, for example, extra pain medications, intra-articular injections, etc. Often, these treatments constituted a major protocol violation, requiring that the patient be dropped from the study. There is a trade-off between patient retention and tolerance of variability in RA trial design. Protocols demanding rigid adherence may yield uninterpretable results because of dropouts and noncompliance emanating from patient and investigator intolerance of the requirements. On the other hand, protocols

permitting any kind of additional intervention may likewise be so confounded as to defy interpretation.

The following strategies may help minimize loss of information:

1) Use screening or run-in periods so that patients are randomized to treatment groups only after their eligibility and commitment is confirmed.

2) Thoroughly train investigators and study personnel to minimize inappropriate enrollments, protocol violations, and other deviations that would decrease the ability to assess trial outcomes.

3) Include dropout in the definition of the endpoint, as in a time to defined treatment failure, or a defined by-patient success or failure.

   One example of this approach would be to use a protocol defined response rate as the primary endpoint. Dropouts, and patients not dropping out, but having minimal or no response to therapy, are classified as nonresponders. With this type of endpoint, the criteria for classification as a nonresponder need to be clearly and prospectively defined. **[Issue for Advisory Committee members: Is this approach appropriate?]** [Illustration: In a study of 6 months duration the primary endpoint could be a comparison of the proportion of patients with an ACR 20 response at six months. Such a protocol might specify that if no more than 15% improvement compared to baseline were seen on two consecutive study visits after two months on protocol, the subject would be declared a nonresponder. Nonresponders could be removed from study drug, and changed to an alternative treatment if desired by physician and patient, but would continue to be followed until the end of the study.]

4) Make provisions for following patients who have stopped experimental treatment. Options include allowing a protocol specified crossover to a standard therapy, for patients meeting predefined criteria for treatment failure.

5) Allow more flexibility in treatment options during the study. Some designs that have been used include allowing dose adjustment of the comparator arm (assessor and patient blinded); allowing add-on therapy for patients meeting predefined criteria for inadequate response, and allowing a limited number of joint injections, with elimination of that joint from assessment.

2. Trial designs in RA

Clinical trials in RA can be designed to test a difference - demonstrating that the investigational product is superior to control (placebo, lower test dose, another active agent), or they can be designed to test an equivalence claim - demonstrating no difference in efficacy from active control. Placebo-, dose-, concentration or active-controlled designs are acceptable. It is desirable that at least one study show an unequivocal treatment effect, i.e., the test drug has better efficacy than a randomized control arm, whether the control arm is a lower dose of the agent, an "active" control, or a placebo.

a. Superiority trials

The standard two arm, investigational agent versus placebo design has been the most common RA design and is the most straightforward. The details of trial design will depend on the population tested. Patients with mildly active RA taking only NSAIDS, who have never been treated with an additional class of therapy, may be enrolled in a placebo-controlled trial with continuation of NSAID background therapy; however, patients doing poorly on NSAIDs alone are usually not appropriate candidates for placebo controlled trials. The same considerations apply to patients who are partial responders to, or who have failed, various other treatments.

Alternative versions of the two arm difference design are a standard dose response study, and a superior to active control hypothesis. These designs may accommodate the need to provide active treatment to patient groups where randomization to placebo is not feasible.

b. Equivalence trials

Equivalence trials are designed to support a claim of effectiveness by showing that the investigational drug is most likely as effective as an active control. The criteria for determining equivalence should be prospectively stated and should be based on achieving 95% confidence that the real difference is smaller than a predetermined amount. Standard confidence limit statistical techniques should be used. Achieving similar point estimates of the efficacy of the two agents is ***not*** a demonstration of equivalence. Equivalence trials usually require more patients to achieve adequate power than difference trials.
A major problem in equivalency trials is assuring that both treatments were equally effective rather than equally ineffective. Approved agents for RA have fairly small effects and frequently fail to show efficacy when tested against a placebo. Comparative trials intended to show "equivalence" to such treatments, when not anchored by a placebo control group, may lack credibility. It is desirable in equivalence designs to select highly effective comparative agents used in the optimum dose and patient population. If possible, use of a third (placebo or lower dose) arm, so that a treatment difference can be shown, is a desirable strategy in equivalence trials. This arm would not necessarily have as many patients or as long a duration as the active comparators. It is important to design both efficacy and safety measures in a manner that is not biased against the control to ensure a "fair comparison."

Trial conduct that adds to the inherent variability in the outcomes may obscure differences and thus lead to a false conclusion of equivalence. This is the opposite of a difference design, where sources of variability work against trial success. For this reason, minimizing dropouts, patient non-compliance, and missing data is essential to the credibility of the study.

[Example of a statistical equivalence test: As an example of these design decisions, consider the setting where response rates to methotrexate (in methotrexate candidates) with measures such as the ACR 20% are estimated to be on the order of 50%. In this setting, new agents studied in equivalence designs with the methotrexate control might, for example, be expected to show a responder rate around 50%, with a 95% confidence interval or window in the range of up to $\pm$ 20%. In other words, if the agent shows the lower bound of the response rate within 20% of the active control response rate result, and if both the test and

methotrexate statistically exceed the response rate for a negative control arm, equivalence would be declared. 80% power calculations to determine sample sizes, given the null hypothesis of not more than a 20% difference of two agents assumed equivalent, yields a figure in the range of 125 patients per arm.]

As noted above, requirements for patient number and/or trial duration are usually more demanding for equivalence trials compared with difference trials. Proposals for equivalence trials will be considered by the Agency on a case-by-case basis, depending on the particular agent of interest, the positive control used, the outcomes measured, and the patients enrolled.

c. Trial designs novel to the study of RA

The following designs have not been traditionally used in the study of new RA treatments, but may be considered in certain circumstances.

1) Withdrawal designs. The withdrawal design -- in which patients in both arms of a study are treated with the investigational agent, which is then blindly withdrawn from one arm, after which patient outcomes are compared -- is sometimes used to assess efficacy. Demonstration of statistically significant worsening in patients taken off the investigational drug demonstrates effectiveness. Natural endpoints for withdrawal designs are "time to (predefined) worsening" using standard "time-to-occurrence" statistical tests, or a simple comparison of proportion of outcomes in the two arms. Withdrawal studies may be performed with both arms on background therapy.

2) Induction designs. **[Issue for Advisory Committee members: FDA would like advice on the evaluation of short-term administration of agents that are intended to have longer term results--hence the term "induction."]**

3. Analytical Issues

a. Handling Dropouts.

Historically, inferences from RA trials have suffered from diminished reliability because of information loss due to dropouts. Dropouts probably never occur randomly, and rarely occur fully independent of the treatment being tested, so there is always the possibility that dropouts introduce a bias. This problem is common in many randomized trials. There have been methods proposed for analyzing the effects of dropouts, but none is fully adequate. An approach with the potential to deal with this problem is to follow all patients, including dropouts, to the planned trial endpoint (even if post dropout information is confounded by new therapy).

This problem is not solved by using the "intent-to-treat" (i.e., all randomized patients included) analysis with an imputation by "last observation carried forward" (hereafter called ITT/LOCF), nor by showing that ITT/LOCF and PP/OC (per protocol completers/observed cases only) analyses concur.

Thus, the effects of dropouts should be addressed in all trial analyses to demonstrate that the conclusion is robust. This may be accomplished by showing the result holds despite application of the "worse case rule" - assign all post-dropout scores for placebo patients the best score, and for all for the drug patients the worst score.

b. Comparison to baseline outcome measures

A phenomenon frequently observed in RA, as well as other conditions, is that patients who stay in trials do better than those who drop out: "Responders do better than non-responders." This is true for both placebo groups and active treatment groups. If observations of the disease were made exclusively from clinical trials, one might conclude that the natural history of the disease is inexorable improvement. This phenomenon is attributable to preferential dropout of worsening patients (a phenomenon not adequately compensated for in LOCF analysis) as well as "regression to the mean." The problem is exacerbated in flare designs, where all patients have major improvement regardless of treatment status. This fact makes comparison-to-baseline outcome measures very difficult to assess, since, very often, much of the improvement noted has no relationship to a treatment effect. For these reasons, active controlled trials not incorporating a placebo arm, and using comparisons to baseline,

may be extremely difficult to interpret, especially if a flare design is employed.

4. Statistical Considerations in Efficacy Trial Design

It is advisable to discuss the design and analysis with the FDA review team prior to embarking on a study. In addition, FDA's Guideline for Format and Content of the Clinical and Statistical Sections of New Drug Applications contains useful information.

a. Randomization/Stratification

The purpose of randomization is to allocate patients to treatment groups to assure that unbiased estimates of differential treatment effects exist, since it is not possible to predict all influential factors.

In some clinical trials, there are known factors that are at least as influential in controlling the observed severity of disease as the drugs being studied. Stratification may be used to avoid relying on randomization properties to balance patient assignment for these factors. Stratification is implemented by constraining simple randomization to balance the assignment of patients to treatment groups for the chosen stratification factors.

Every Phase 2 and Phase 3 study protocol should contain a randomization section. All constraints imposed on the randomization should be explicitly identified. It can then be inferred, when a stratification factor or sample size allocation constraint is not mentioned in a protocol, that there exists no corresponding randomization constraint. This applies to whether patients are blocked to balance treatment assignment for time of patient entry into study and to the more obvious stratifications on center and baseline.

Because stratification implies constraints on randomization, studies that have been stratified for certain factor(s) should account for these factors in the statistical section of the study protocol. The protocol analysis should be implemented for each study.

There are also statistical procedures to address bias in treatment group comparisons by adjusting for imbalances in pre-specified factors (covariates).

It is not required that randomization be stratified; however, failure to stratify can be unwise. In all clinical trials, practical judgment is required in deciding when to stratify. There are reasons to choose stratification and reasons to choose statistical adjustments.

1) The advantages of stratification are, first, that it is better to avoid possibly major statistical adjustments of differential treatment effects. Stratification would essentially eliminate the effect of such adjustments before analysis began. Second, although stratification and statistical adjustment procedures are both designed to remove bias in estimated treatment effects, stratification is more powerful. This is because stratification leads to smaller variances of estimated treatment effects than does statistical adjustment without stratification. Finally, the inclusion of stratification factors into a statistical analysis model should result in increased power to detect effectiveness.

2) Stratification becomes increasingly clumsy as the number of strata increases, and consequently, the available number of randomizable patients per cell decreases. It is logistically simpler not to stratify, relying on statistical methods to adjust for the minor imbalances usually resulting from failure to stratify.

   The best approach may be to combine stratification, applied to a limited number of the most influential prognostic factors, with statistical modeling. Statistical modeling would account for stratification and would be used to adjust for the effects of a parsimonious number of the most important remaining factors.

b. The Identification of Primary Efficacy Variables

Each Phase 2 or Phase 3 study protocol should identify the primary and secondary efficacy variables. Primary efficacy variables are critical to the identification of the effectiveness of the product. It is for the primary efficacy variables that statistically significant results are expected to confirm the superiority or the clinical equivalence of a product. Secondary efficacy variables are those which support the validity of the primary variables but which are not critical in deciding if this product is effective. It is helpful, but not necessary, that statistical evidence of efficacy be shown for secondary efficacy variables.

c. Prespecification of Statistical Analysis

Statistical analysis of primary clinical endpoints is part of the process for obtaining consistent and convincing evidence of product efficacy. These statistical analyses should not be data driven. In part, this is implemented by identifying, in each study protocol, before data are available for analysis, a sufficient description of the statistical analyses of these primary efficacy variables so that an independent statistician could perform the protocol analyses. This description of the statistical analyses should include but not necessarily be limited to specifying (1) what constitutes the minimal statistical results needed to demonstrate a successful outcome, (2) whether statistical tests of hypothesis or confidence intervals will be 1- or 2-sided, (3) what level of significance is to be used, (4) how missing values and dropouts are to be handled, (5) the mathematical expression of the statistical model used, and (6) the planned multiple treatment comparison method.

d. Multiple Endpoints

1) Many RA studies use multiple endpoints to assess primary evidence of effectiveness. For example, for the four measures recommended in FDA's previous guideline, trial results were considered to support a conclusion of effectiveness when statistical evidence of efficacy was shown for at least 3 of the 4 measures: physician global assessment, patient global assessment, swollen joint count, and painful joint count.

2) Multivariate statistical methods are also available for analyzing the set of primary efficacy variables.

3) Efficacy variables can be combined within patients (composite endpoint). Such a fixed combination of efficacy measures should be well defined in the study protocol. Composite efficacy variables have the advantage of avoiding several statistical and inferential difficulties associated with multiple endpoints.

e. Dropouts

Dropouts are patients who, after a certain period of time in a trial, fail to provide clinical efficacy data scheduled by protocol to be collected. Frequently, dropouts occur for reasons related to taking the assigned test drug (adverse effects or lack of efficacy). Since dropouts do not usually occur randomly, the remaining patients constitute a biased sub-sample of the patients originally randomized.

Methods used to handle dropouts, such as the "LOCF" and "completers" analyses are not fully satisfactory even though they have often served as the basis for determining that adequate statistical evidence of efficacy has been provided. The LOCF method generally does not preserve the size of the test, either for the comparison of final observations or for the comparison of rates of change. Alternative methods include growth curve analysis and random effects regression. These are also susceptible to informative censoring--that is, dropping out depends on the value of the response. It is often useful to show that the results hold for a variety of analyses--i.e., they are robust.

f. Trials with Several Treatment groups/Multiple Comparisons

In clinical trials involving more than two treatment groups, a statistical multiple comparison procedure controlling the experiment-wise error rate to 5% or less should be applied. In essence, there should be overall statistical evidence of a treatment

main effect before attempting to make specific drug comparisons relevant to proposed drug labeling.

g. Interim Analyses

Interim analyses are those which, for any purpose, are performed on partially accumulated clinical trial efficacy data. The study protocol should state whether such interim analyses are planned or not planned. Should interim analyses be planned, that plan and its implementation should be described in the protocol. The protocol should identify the scheduling of these analyses, the method to be applied for adjusting significance levels, and the corresponding time sequence of significance levels at which statistically significant results will be claimed.

While an interim analysis may not be thought to affect the subsequent collection of efficacy data, interim analyses carry an additional risk that the blinding or conduct of a study may have been compromised. Because multiple tests (including interim analyses) alter the true significance level, methods have been developed to compensate for this phenomenon. These statistical methods cannot compensate for any unblinding and bias that may result from gathering the information needed to perform an interim analysis.

h. Sample Size

Failure to recruit an adequate number of patients is a major reason why an effective drug product may fail to meet established statistical criteria for efficacy, independently of whether the purpose was to show superiority or comparability of treatment effect. The method of determining the sample size should be stipulated in sufficient detail to permit independent verification of the computation. This should include identifying the efficacy variable the sample size determination is based upon, the magnitude of the clinical difference to be detected, the power, the significance level, and the sidedness of the statistical procedure(s) described in the analysis plan. Furthermore, the size of the clinical difference chosen should be justified and the choice of the efficacy variable used to determine sample size should be discussed briefly.

i. Trials to show Clinical Equivalence

The words "clinical equivalence" are used in a much more narrow sense than these words might imply to the casual reader. First, there is often no intent of showing equivalence of two or more drugs across the broad spectrum of pharmacologic effect. Rather, focus is on showing no clinically relevant differences for one or possibly more variables which are to be clearly identified in advance. The concept of equivalence is two-sided in that if, for any outcome measure, one drug is sufficiently different from another drug, then these drugs are no longer deemed equivalent in that variable.

To show equivalence, the variables serving to measure these effects of interest should be defined in the protocol. For each efficacy variable for which clinical equivalence of effect is sought the magnitude of a difference deemed to be inconsequential should be identified. The clinical data should then show, with 95% confidence, that this pre-defined difference is not exceeded.

Inference based on trials to show equivalence is inherently less convincing than inference based on trials to show the existence of a difference. Often clinical trials do not detect treatment differences which are known to exist. In such cases, statistical methods may then seemingly provide evidence of equivalent effect, e.g., to placebo.

In cases where a per patient success rate can be established, equivalency may be demonstrated if the two sided 95% confidence interval of the test group does not exceed $\pm 10\%$ of the control group rate ($\pm 15\%$ of a control rate of 85% or lower, or $\pm 20\%$ of a control rate of 80% or lower). **[Issue for Advisory Committee members: FDA seeks your advice on these intervals. Is potential loss of 20% of the active control effect acceptable? Is the interval too tight? Is the reference to scales understandable?]**

In cases where individual scales are used, 95% confidence intervals that are contained within a 10% range (around the control value) of the total used portion of the scale are generally recommended.

j. The Role of Statistical Significance

Drugs are approved on a weighing of risks and benefits. Rejection of a null hypothesis of no drug effect is evidence that a drug effect does exist. This does not necessarily imply that the effect thus detected is adequate. The magnitude of difference in drug effect that is clinically meaningful should be addressed in the protocol and discussed in advance with FDA representatives.

k. Types of efficacy endpoints

The goal of the statistical analysis of the endpoint is to demonstrate if the product shows convincing evidence of efficacy. Studies of RA generally involve measurements taken at several times, and statistical methods appropriate to this design need be employed. The primary efficacy variables should be specified in the protocol for the study and the proposed analysis should be outlined. In the analytical plan, the method of determining the sample size should be stipulated in sufficient detail to permit verification of the computation. There are several options for endpoints available:

1) The response may be a binary variable indicating improvement from baseline. The analysis here has a straightforward interpretation if all patients are included to completion. If some patients have only partial follow up, it may be unclear how they should be scored unless the procedure is specified and justified in the protocol.

2) The response may be an ordered categorical one (e.g., much worse, worse, no change, better, much better). Such responses are usually analyzed using ranks (accounting for ties), leading to a Wilcoxon rank-sum test. The response is measured at the specified ending time of the patient regimen. If patients fail to complete the regimen, there is no clear way to impute the subsequent time point data.

3) The response may be a continuous variable (e.g., time to an event, the tender joint count), and the difference between final and baseline used ("change score"). This widely used method has the advantage of measuring a clinically recognized difference, but it does not account

for time. By dividing the change score by the time interval, a rate of change per unit time is obtained, which allows inclusion of data from all patients whether they complete the study or not. Similarly, one could determine the best fit slope for each patient's measurements.

l. Appropriateness of the statistical methodology

The appropriateness of the statistical model should be assessed, including checking for outliers and determining if distributional assumptions (usually normality) are met and if common variance assumptions hold homoscedasticity.

m. Site effects

If the patients have been stratified and randomized by site, the analysis should include a site effect. There may be a site by treatment interaction reflecting the degree to which the treatment varies across sites. This is often notable when there is a great variation in enrolled patients across sites. Site by treatment interaction should be explored.

F. Safety Analysis

The approach to evaluating adverse reaction data and laboratory values has traditionally differed from that used to evaluate efficacy. The purpose of safety evaluations is usually not to test a specific hypothesis, but rather to examine the pattern of effects and to detect unusual or delayed events. Analyses using cumulative occurrences, scatter-plots of laboratory values (baseline versus on-therapy), or general regression techniques may be helpful. The safety profile should address to what extent adverse events (drug reactions or lab values) depend on duration of drug exposure, dose level, coexisting medical conditions, or possible drug interactions. Incidence rates should be calculated using denominators that reflect the period of drug exposure for the population at risk. Cumulative incidences (hazard rates, instant probabilities) better represent the temporal pattern of drug effects than do prevalence rates, and comparative cumulative incidence tables drug versus active control(s) versus placebo, are very helpful to practitioners.

1. Intrinsic trial design considerations

An attempt should be made to characterize the patient population susceptible to adverse drug effects. Some extraneous factors can complicate the safety data, such as variations in soliciting and reporting adverse events among the investigators, and differences in the definition of normal ranges for lab values among different laboratories. Since adjustment for their effects may be difficult, precautions should be taken in the design stage of the trial to minimize the influence of these factors by preparing clear and specific instructions for data collection, and monitoring adherence of the investigators and the laboratories to the protocol. Procedures for normalizing laboratory data, for example, may be employed. As previously mentioned, developing standardized toxicity grading scales that may be employed in all studies may also be useful.

2. Adequate numbers

The ability to detect adverse experiences is dependent on the number of patients evaluated in the clinical trials and in clinical usage. Studies of less than 300 patients per group do not have the statistical ability to necessarily detect adverse experiences in that group of less than 1%. In most cases however, it is permissible to combine studies of equal duration to establish adverse experience rates.

For any chronically administered product, the safety data base should include at least 300 patients treated with the maximally recommended dose for at least 6 months and at least 100 patients treated for at least 12 months (ICH Guideline for Industry: The Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions, March 1995 (ICH Safety Guideline)).

[Issue for Advisory Committee members: What is the appropriate size of the safety database. The CDER Guideline for the Clinical Evaluation of Anti-inflammatory and Anti-rheumatic Drugs (1988) calls for 200-400 patients for one year and 100-200 for two years. (This is considered desirable for the safety evaluation of NSAIDs in particular, because of their known adverse event profile). The "DMARD" portion of this guideline calls for 400 patients for one year and 200 patients for two years. The ICH Safety Guideline allows exceptions for classes or examples of drugs with known or potential safety problems. To what extent is the ICH recommended

safety database adequate for evaluating the safety profile of various RA treatments?]

G. Informed Consent

In each case it is important that informed consent be complete and that patients be able to understand what they are consenting to. If the potential exists for disease exacerbation, this should be part of the informed consent.

III. SPECIAL CONSIDERATIONS FOR BIOLOGICAL PRODUCTS

Although there are similarities between RA trial designs for drugs and biologics, biologics have special characteristics and problems that should be considered in their development.

A. Species Specificity

The schemes used traditionally in determining the initial human dose may not pertain to biologics. Biologic agents may behave differently in animal models than in humans, depending on the physiologic relevance and avidity for the receptor of the ligand in the animal compared to the human.

B. Dose Responses

The dose response curve may be steep (narrow therapeutic window) and/or even hyperbolic, and an agent can be quite toxic at levels just above those thought to show efficacy.

C. Toxicity Response

The toxicity response curve may be highly unpredictable and potentially very dangerous, and include the risk of disease worsening. Biologics may have the potential for disruption of immunologic and physiologic processes. Monoclonal antibodies to cellular epitopes of the immune system, for example, or to TNF receptors, can or may cause serious morbidity at doses only slightly higher than those that are efficacious with markedly less toxicity.

D. Product Homogeneity

This often plays a critical role in activity and toxicity of a compound. Product alterations can greatly affect physiologic activity. Thus, biologics should have consistent lot-release criteria and be reasonably well characterized to be properly evaluated.

E. The Role of Neutralizing Antibodies

If Phase 2 data suggest that agent-induced neutralizing antibodies may interfere with the efficacy of a biologic agent over time, it may become necessary to formally investigate the possibility in a randomized controlled setting. The occurrence of neutralizing antibodies may require reconsideration of doses and dose regimens.

IV. SPECIAL CONSIDERATIONS FOR MEDICAL DEVICES

A. Background

Medical devices for the treatment of RA vary considerably in their therapeutic intent, ranging from agents designed for primary therapeutic effectiveness to those utilized as therapies adjunctive to drugs or biological agents. The variability in therapeutic effects due to disease and response heterogeneity may be more problematic with devices than with drugs and biologics. Preclinical testing requirements cannot be generalized because devices for RA have a diverse range of chemical, mechanical, and electrical properties. In addition, the issues of the optimal placebo control and of local versus systemic effects are common in the evaluation of medical devices. These factors are relevant to both efficacy and safety determinations as described below.

B. Efficacy Considerations

1. Some medical devices intended for local administration may have unexpected systemic therapeutic effects, so precise determinations of mechanisms of action should be made to minimize this phenomenon.

2. Use of a "sham" device is the most desirable placebo control for medical devices, but the success of patient and/or physician blinding with sham devices is not always complete. Blinding may not be feasible if the product is delivered in a surgical or invasive medical procedure. Since inadequate blinding usually biases efficacy determinations in favor of therapy, *design of adequate blinding and its monitoring is imperative.*

3. For devices intended to be utilized as adjunctive therapies to drugs or biologics, design approaches and analysis methods should balance or account for the differences in disease status and severity, in order to minimize biases in endpoint outcomes. Similarly, the primary therapy with drug or biological agent should be consistent to avoid outcome bias, as should additional, possibly confounding co-therapy (hot/cold therapy, splinting, physical therapy, orthotics, etc.)

4. The issue of quality of life (QOL) determinations is very important for devices intended for rehabilitative purposes, particularly if there are substantial technical demands of certain device uses. Device QOL benefits should be judged by their ease and convenience of administration by assessing the satisfaction with therapy and the improvement in QOL. The outcomes of these determinations should be blinded from the participating investigators to avoid assessment bias.

5. For devices necessitating in-hospital or in-office use, it is recommended that clinical utility be determined accurately and early in development. In addition to adverse event risks, the practical "risks" of the product, such as inconvenience or pain with administration, should also be characterized and judged as efficacy outcomes. Although it is difficult to gather reliable efficacy data, let alone clinical utility, early on, this is critical for the sponsor in order to be able to make a reasoned "go/no go" decision. Agency consultation is advisable.

C. Safety Considerations

1. The availability of well-characterized short-term adverse event rates (3-month cumulative incidence of about 1%), as described for drugs, may not be feasible for medical devices. Due to the more technically demanding administration of devices, it is generally not feasible to enroll large numbers of patients or to conduct several concurrent studies. The timing of device adverse events may differ from that of drugs in that common adverse events may not occur frequently within the first few months of treatment. Therefore, patients with devices which have a delayed effect noted in preclinical or Phase 2 testing should have extended follow-up beyond time on device. These factors may constrain the ability to capture adverse events needed to build an adequate safety database, and may therefore need to be addressed in post-approval studies designed to increase the duration of follow-up or increase the numbers of patient exposures.

2. Because some medical devices are administered in conjunction with a medical or surgical procedure, the distinction between a device-related or procedure-related adverse event is sometimes obscure. The nature, timing, and degree of severity are some factors used to help determine whether an adverse event is device- or procedure-related. These determinations are often based on clinical judgment, so if blinding is inadequate a potential for bias exists. For this reason, the evaluator should be blinded to treatment (i.e., segregated treating and evaluating

physicians). It is recommended that sponsors detail protocol guidelines for assessing procedure-related versus device-related adverse events.

3. Although some medical devices (e.g., those emitting radiation or those administered with a procedure) for RA treatment may be used intermittently, some may be intended for chronic use, so identification of a maximum lifetime exposure or a maximum frequency of exposure to the device is important.

V. SPECIAL CONSIDERATIONS FOR JUVENILE RHEUMATOID ARTHRITIS

A. Background

Juvenile rheumatoid arthritis is a heterogeneous group of diseases which share the common feature of chronic, idiopathic inflammatory synovitis, with onset prior to 16 years of age. These disorders have been divided into clinically distinct subsets based on the extent of joint involvement and extra-articular manifestations: pauci-, poly-, and systemic-onset JRA, as well as oligoarthritis associated with HLA-B27, and they have been further subdivided based on clinical courses.[7] Immunogenetic subsets appear to correlate with these clinical course subsets, and are also distinct from adult RA.[8] (The HLA-B27 subset is not addressed in this document.) Of these various entities, polyarticular JRA is similar in many aspects, particularly in clinical signs and symptoms, to adult RA. While the other JRA subsets are clinically distinct, it is notable that the synovitis seen in any of the JRA subsets appear to be clinically indistinguishable from adult RA, including similar efficacy responses to existing pharmacotherapy (NSAIDs, methotrexate, and prednisone).[9] As only 3-5% of all patients with rheumatoid arthritis develop illness onset during childhood, many investigational therapeutic agents in this population will therefore receive orphan drug status, according to 21 CFR Part 316 - Orphan Drugs. The application of principles in the conduct of clinical trials for adult RA largely applies as well to JRA, and this section only outlines those areas of difference from adult RA.

Conducting drug studies in children is generally necessary and consistent with the expectations of treatment regimens for this disease. Because pediatric subjects constitute a vulnerable population, conducting research involving minimal risk is important. The Committee on Drugs of the American Academy of Pediatrics has published guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations,[10] and general considerations for the clinical evaluation of drugs in infants and children,[11] both of which should be consulted. Guidelines regarding informed consent and assent of pediatric patients from the Committee on Bioethics of the American Academy of Pediatrics should also be followed.[12] Conducting clinical trials for patients with

JRA, and particularly assessing global disease activity and response to therapy, should involve pediatric rheumatologists or adult rheumatologists who have extensive training in pediatric rheumatology and have demonstrated competence in caring for children with rheumatic diseases.

As a general principle children should not be subjected to an agent that has not been first tested for safety in adults. Testing may begin in children, however, when the anticipated benefits based on existing knowledge may justify the anticipated risks. An agent developed specifically for use in JRA (e.g., a biologic agent targeted against a specific pathogenic process which is unique to JRA, and not present in adult RA) may need to be tested first in children, as exposure in adult RA patients or even normal adult volunteers may be unrevealing. If, however, the agent has potential for use in both adult RA and JRA, then, at minimum, pK-pD and initial Phase 1 data (including maximum tolerated dose) should be available for adults prior to the start of testing in children. JRA trials of drugs that are expected to be similar in efficacy to existing drugs, and which do not represent major therapeutic advances or alternative approaches to the basic mechanism of intervention can be delayed until there is extensive efficacy and safety data from either adults or in other pediatric populations.

The need for reliable inferences does not necessitate a placebo control, but randomization and controls should be employed. The choice of control is a function of what is known about the agent at the time and what other treatments are available to potential trial enrollees. If only an active control is used for an equivalence trial, convincing evidence of the efficacy of the active control should be provided, and the test proposed to establish equivalence should be specified. If there have been no prior adult studies, or if the agent under development has a novel mechanism of action or represents an entirely new class of drug, a randomized, double-blind trial, using either a placebo or an active control group of (anticipated) similar efficacy is indicated. Open label extensions to obtain additional data about risk and persistence of benefit are very valuable. The use of active control (standard of care therapy) in the control arm, dose-response design (where control receives a lower dose(s) of the test agent), crossover, or, if the agent has a short onset of effect, randomized placebo-phase trial designs are encouraged as possible alternatives to inactive placebo control in JRA studies. As a general principle, protocol escape clauses are encouraged to permit children who are not responding well to experimental therapy to receive early conventional or alternative treatment. However, when escape clauses are inserted, the sponsor should also indicate how such dropouts will be handled in the analysis.

B. Applicability of the Pediatric Regulation and Impact on Trial Design for JRA Studies.

The "pediatric use" section of labeling regulations (21 CFR 201.57) permits drug and biologic products to be approved for JRA if they have been demonstrated to be safe and effective for adult RA and the disease and mechanism of action of the drug are sufficiently similar in children. Although the regulation allows extrapolation of adult efficacy data, usually additional pediatric dosing and safety evaluations are needed. The following applications of the pediatric labeling rule are applicable to JRA clinical trials. In all cases, application of the pediatric rule may be applied to the signs and symptoms claim only; other claims, including quality of life, radiographic progression, and remission, should have separate JRA efficacy studies. The label should reflect the specific studies performed and documentation provided (efficacy studies in all JRA subsets, or safety and pK studies only in polyarticular JRA, without demonstration of efficacy), in accordance with the regulation.

1. For currently approved agents, including traditional NSAIDs which are cyclooxygenase inhibitors, methotrexate, and corticosteroids, adequate efficacy information exists for all JRA and all JRA subsets. For such agents, a labeling claim could be supported using only pharmacokinetic, pharmacodynamic and safety data in JRA patients, although submission of additional JRA efficacy data is encouraged.

2. For agents currently approved for adult RA, which are not approved for JRA, including auranofin, gold sodium thiomalate, hydroxychloroquine, and pencilliamine, adult efficacy data can be used to support a signs and symptoms claim for polyarticular JRA. There is not adequate data to support extension to all JRA subsets. Pediatric safety and dosing studies of adult data should be submitted to support a label claim for polyarticular JRA. The agency should be consulted to assess the need for any additional studies.

3. For new agents not yet approved for adult RA, adult efficacy data can be used to support a signs and symptoms claim for polyarticular JRA if there is biologic plausibility that the agent would have a similar effect in JRA. When evidence for biologic plausibility does not exist, evidence should be submitted to support the application of the pediatric rule (the agency should be consulted in determining whether adequate biologic plausibility exists to apply the pediatric rule). Pediatric safety and dosing studies should be submitted. The extent of safety testing will depend on the agent, its prior use and any established safety in other

pediatric populations. It is desirable that as much efficacy evidence as possible be gathered during the evaluation of pediatric dosing and safety.

4. It is preferable that efficacy studies be performed in JRA for the signs and symptoms claim, including agents for which biologic plausibility of a similar effect in JRA exists and other categories listed above. Sponsors who seek approval for all JRA should include all JRA subsets in an efficacy study. The data could support a claim for JRA (subsets not specified) provided that the data do not suggest that the agent is ineffective in any one subset. The label should reflect that efficacy was demonstrated, and that the agent is approved for JRA (subsets not specified).

   When the pediatric regulation is applied, the need for pharmacokinetic, pharmacodynamic, and safety studies may still remain. Separate pK-pD studies are not needed for each JRA subset, although all subsets should be represented in such studies. However, due to greater toxicities associated with drug treatment of systemic-onset JRA,[13] [14] [15] strong consideration should be given to conducting studies which allow for stratified analysis of this subset of JRA. If data are available and the coefficients do not differ significantly for adults and children, then the number of time points at which specimen collection is done can be reduced to the minimal number to confirm the curves observed in adults. Micro-sampling techniques should be employed for such studies.

C. Outcome Variables and Claims

It is possible for sponsors to seek approval for all JRA subsets, or to seek approval for individual subsets. In the former case, the label should note the trial numbers in each subset and character of each subset response. Except as noted above in the application of the pediatric rule, all claims should be supported by an efficacy demonstration in the intended subset(s).

1. Clinical Signs and Symptoms:

   All JRA trials should evaluate improvement based on the definition of improvement established by the JRA core set: 3/6 (MD global, parent/patient global, number of active joints, number of joints with limited range of motion, functional ability, and ESR) improved by at least 30% and no more than 1/6 worsening by more than 30%.[16] Protocol individualization may necessitate a refinement in the responder test for patients: for pauci-articular JRA, with, for example, one knee involved and a normal ESR, use of joint and functional assessments

specific to the involved joints, and evaluation of uveitis as co-primary endpoints may also be valuable.[17] For patients with systemic onset JRA, additional assessment of fever, extra-articular manifestations, and thrombocytosis/leucocytosis may be useful co-primary endpoints.[18] Outcome variables need to be clinically "sensible" and appropriate to the type of agent under investigation. Investigators should decide a priori how much change is considered clinically important for each outcome variable.

In all cases, trials should be at least three months, and some assessment weighing all time points equally should be used.

2. Function/Quality of Life

This claim is proposed to reflect demonstrated improvement in function and health related QOL, for six consecutive months, and demonstrated success in signs and symptoms over the same period. This is currently obtainable only in principle, as adequate methodology is not yet at hand. Endpoints will need to be tailored to subtypes enrolled in trials (e.g., to assess knee function in pauci-articular JRA patients who may have this as their primary arthritic manifestation). Instruments should be developmentally validated for the age ranges studied in a trial.[19]

3. Prevention of Structural Damage

Similar to adult RA, this claim would reflect trials of one year or more with concomitant success in signs and symptoms. Currently, only sparse data exist regarding the usefulness of only one radiographic measure in JRA: the carpal-metacarpal distance in those patients with wrist arthritis.[20] Other clinically promising settings include the evaluation of erosive disease in systemics with polyarthritis, hip assessment in systemics, and knee assessments in pauci-articular JRA.

4. Complete Clinical Response

The claim of complete clinical response reflects achievement of six consecutive months of morning stiffness of less than 15 minutes duration, no active synovitis (pain, redness, tenderness to palpation, swelling, stable or decreasing limitation of motion), no extra articular features (including fever, serositis, adenopathy, hepatosplenomegaly, rash, uveitis), and normal laboratory parameters (including ESR, platelets, WBC) and where applicable, no ongoing structural damage while continuing on therapy. Trials should be of one year duration.

Residual damage from prior disease, including extra articular manifestations, is acceptable in meeting criteria for complete clinical response. Because complete clinical response rates may be relatively high in JRA, these studies should be controlled. The need for ongoing therapy may be undesirable if the toxicity of the agent is unacceptable.

5. Remission

Remission is characterized exactly as above, but off drug.

6. Major Clinical Response

[Need Advisory Committee input on this claim and its feasibility]

Patients with chronic synovial thickening without clinically active synovitis (stable synovial thickening) show limited but stable range of motion but may have pain so they would not qualify as a complete clinical response/remission. A "major clinical response" claim for these patients (analogous to this claim in adult RA), represents a response more important than signs and symptoms but less than a complete clinical response/remission. This claim has not yet been fully defined, but it is expected to be a "data driven" definition, similar to the adult RA definition.

D. Trial Design Issues

Recommendations for efficacy studies are based upon the nature of the agent under development. The principles outlined for adult RA are generally applicable. Patients enrolled into these trials may be of any onset or disease course subset. Separate trials for each JRA subset are recommended if the agent is predicted to have a target mechanism of action that will not be applicable and equally efficacious in all JRA subsets. Alternatively, a single, sufficiently large trial with enrollment appropriately stratified provides for useful conclusions to be reached about efficacy and safety for each subset. Co-variates (for adjustment in the analysis) should include, at a minimum, disease course type, disease duration, and non-response to prior methotrexate. Given that JRA is an orphan disease, there is often some flexibility in trial design, but this should be discussed on a case-by-case basis.

At this time, JRA patients should not usually be eligible for entry into efficacy trials unless they have failed to respond adequately to at least one standard "second line agent" (such as methotrexate at a dose of at least 10 mg per meter squared body surface area per week). There may be exceptions to this if, for

example, there is evidence that greater efficacy could be obtained by using the agent very early in the disease course, evidence that delayed use in sicker patients potentially carries greater risk of toxicity, or evidence that the agent has a favorable safety and efficacy profile in a comparable population studied to date and that the agent's actions are potentially readily reversible.

Whether or not the patient continues to receive the agent upon discontinuation from protocol, the patient should be monitored periodically for an extended period. Effects on skeletal growth, development, behavior, sexual maturation, reproductive capacity, and secondary malignancy should be included in the monitoring.

E. Concurrent Antirheumatic Agent Administration

The general principles outlined are applicable in that the goal is to limit the use of discretionary concurrent antirheumatic therapies as much as reasonably possible such that total interpretation of efficacy and safety data is not irrevocably compromised. However, limitations of concurrent medication cannot violate ethically justified treatments nor should it make the protocol so unattractive to parents, physicians, and patients that enrollment is threatened. If background treatment is necessary, early tolerance studies, to ensure safety of co-administration, should precede any large trials.

If patients receive concurrent slow acting or prednisone therapy, the dose should be stable prior to study entry, and preferably remain so throughout the trial. Concurrent medications are usually important prognostically and so may need stratification. If possible, intra-articular steroid injections should be disallowed for a minimum of one month prior to beginning experimental therapy; otherwise that joint should be discounted in assessing therapeutic effects.

F. Multi-centered Trials and Center Effects

Although JRA is the most common rheumatic disease of childhood, its prevalence is low compared to adult RA. Thus, trials of JRA that require large numbers of patients will likely be multi-centered. Multi-centered studies should employ a standardized protocol and data collection forms among all centers. Pretrial meetings of all investigators and other involved personnel are strongly encouraged to assure uniformity in protocol interpretation, patient evaluation, and data recording. Studies have shown that, within a cooperative group, a center's performance is a function of the number of patients enrolled at the center.[21] Thus, studies that use fewer centers with greater numbers of patients at each center are preferable to those that use large numbers of centers with fewer patients. Effort should be made to enroll at least 10 to 12 patients at each

center to provide for greater quality assurance. In all multi center trials, center effects should be examined. In such trials, a therapy should show effect in more than one center. When stringent entrance criteria restrict the number of patients eligible for study, many centers may be unable to enroll even 10 patients. In such situations, randomization blocked within individual centers, rather than across all centers, may help to reduce the potential impact of center effects.

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federal register

Wednesday
March 1, 1995

Part X

Department of Health and Human Services

Food and Drug Administration

International Conference on Harmonisation; Guideline on Extent of Population Exposure Required to Assess Clinical Safety for Drugs; Notice

VerDate 31-JAN-95 18:42 Feb 28, 1995 Jkt 156997 PO 00000 Frm 00001 Fmt 4717 Sfmt 4717 E:\FR\FM\P01MR3.PT6 pfrm04

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 94D-0029]

International Conference on Harmonisation; Guideline on the Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a final guideline entitled "The Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-life-threatening Conditions." This guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guideline is intended to present an accepted set of principles for the safety evaluation of drugs intended for the long-term treatment (chronic or repeated intermittent use for longer than 6 months) of non-life-threatening diseases.

DATES: Effective on March 1, 1995. Submit written comments at any time.

ADDRESSES: Submit written comments on the guideline to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. Copies of the guideline are available from CDER Executive Secretariat Staff (HFD-8), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT:
Regarding the guideline: Leah Ripper, Center for Drug Evaluation and Research (HFD-500), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-2544.
Regarding ICH: Janet J. Showalter, Office of Health Affairs (HFY-20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1382.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission; the European Federation of Pharmaceutical Industry Associations; the Japanese Ministry of Health and Welfare; the Japanese Pharmaceutical Manufacturers Association; the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA; and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Association (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

Harmonization of the safety evaluation of drugs intended for the long-term treatment of non-life-threatening diseases was selected as a priority topic during the early stages of the ICH initiative. In the **Federal Register** of March 1, 1994 (59 FR 9746), FDA published a draft tripartite guideline entitled "Draft Guideline on the Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions." The notice gave interested persons an opportunity to submit comments by May 16, 1994.

After consideration of the comments received and revisions to the guideline, a final draft of the guideline was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies at the ICH meeting held in October 1994.

The guideline presents an accepted set of principles for the safety evaluation of drugs intended for the long-term treatment of non-life-threatening diseases. The guideline distinguishes between clinical data on adverse drug events (ADE's) derived from studies of shorter duration of exposure and data from studies of longer duration, which frequently include nonconcurrently controlled studies. The principles discussed in the guideline are summarized as follows: (1) Regulatory standards are valuable for the extent and duration of treatment needed to provide the safety data base for drugs intended for long-term treatment of non-life-threatening conditions; however, there are a number of circumstances where harmonized regulatory standards for the clinical safety evaluation may not be applicable; (2) further investigation is needed about the occurrence of ADE's in relation to duration of treatment for different drug classes; (3) because most ADE's first occur within the first 3 to 6 months of drug treatment, many patients should be treated and observed for 6 months at dosage levels intended for clinical use; and (4) because some serious ADE's may occur only after drug treatment for more than 6 months, some patients should be treated with the drug for 12 months.

In the past, guidelines have generally been issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but are acceptable to FDA. The agency is now in the process of revising § 10.90(b). Therefore, this guideline is not being issued under the authority of § 10.90(b), and it does not create or confer any rights, privileges, or benefits for or on any person, nor does it operate to bind FDA in any way.

As with all of FDA's guidelines, the public is encouraged to submit written comments with new data or other new information pertinent to this guideline. The comments in the docket will be periodically reviewed, and, where appropriate, the guideline will be amended. The public will be notified of any such amendments through a notice in the **Federal Register**.

Interested persons may, at any time, submit written comments on the guideline to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the guideline follows:

The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions

The objective of this guideline is to present an accepted set of principles for the safety evaluation of drugs intended for the long-term treatment (chronic or repeated intermittent use for longer than 6 months) of non-life-threatening diseases. The safety evaluation during clinical drug development is expected to characterize and quantify the safety profile of a drug over a reasonable duration of time consistent with the intended long-term use of the drug. Thus, duration of drug exposure and its relationship to both time and magnitude of occurrence of adverse events are important considerations in determining the size of the data base necessary to achieve such goals.

For the purpose of this guideline, it is useful to distinguish between clinical data on adverse drug events (ADE's) derived from studies of shorter duration of exposure and data from studies of longer duration, which frequently are nonconcurrently controlled studies. It is expected that short-term event rates (cumulative 3-month incidence of about 1 percent) will be well characterized. Events where the rate of occurrence changes over a longer period of time may need to be characterized depending on their severity and importance to the risk-benefit assessment of the drug. The safety evaluation during clinical drug development is not expected to characterize rare adverse events, for example, those occurring in less than 1 in 1,000 patients.

The design of the clinical studies can significantly influence the ability to make causality judgments about the relationships between the drug and adverse events. A placebo-controlled trial allows the adverse event rate in the drug-treated group to be compared directly with the background event rate in the patient population being studied. Although a study with a positive or active control will allow a comparison of adverse event rates to be made between the test drug and the control drug, no direct assessment of the background event rate in the population studied can be made. A study that has no concurrent control group makes it more difficult to assess the causality relationship between adverse events observed and the test drug.

There was general agreement on the following:

1. A harmonized regulatory standard is of value for the extent and duration of treatment needed to provide the safety data base for drugs intended for long-term treatment of non-life-threatening conditions. Although this standard covers many indications and drug classes, there are exceptions.

2. Regulatory standards for the safety evaluation of drugs should be based on previous experience with the occurrence and detection of ADE's, statistical considerations of the probability of detecting specified frequencies of ADE's, and practical considerations.

3. Information about the occurrence of ADE's in relation to duration of treatment for different drug classes is incomplete, and further investigations to obtain this information would be useful.

4. Available information suggests that most ADE's first occur, and are most frequent, within the first few months of drug treatment. The number of patients treated for 6 months at dosage levels intended for clinical use, should be adequate to characterize the pattern of ADE's over time.

To achieve this objective, the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5 percent to 5 percent). Usually 300 to 600 patients should be adequate.

5. There is concern that, although they are likely to be uncommon, some ADE's may increase in frequency or severity with time or that some serious ADE's may occur only after drug treatment for more than 6 months. Therefore, some patients should be treated with the drug for 12 months. In the absence of more information about the relationship of ADE's to treatment duration, selection of a specific number of patients to be followed for 1 year is to a large extent a judgment based on the probability of detecting a given ADE frequency level and practical considerations.

One hundred patients exposed for a minimum of 1 year are considered to be acceptable to include as part of the safety data base. The data should come from prospective studies appropriately designed to provide at least 1-year exposure at dosage levels intended for clinical use. When no serious ADE is observed in a 1-year exposure period, this number of patients can provide reasonable assurance that the true cumulative 1-year incidence is no greater than 3 percent.

6. It is anticipated that the total number of individuals treated with the investigational drug, including short-term exposure, will be about 1,500. Japan currently accepts 500 to 1,500 patients; the potential for a smaller number of patients is due to the postmarketing surveillance requirement, the actual number for a specific drug being determined by the information available on the drug and drug class.

7. There are a number of circumstances where the harmonized general standards for the clinical safety evaluation may not be applicable. Reasons for, and examples of, these exceptions are listed below. It is expected that additional examples may arise. It should also be recognized that the clinical data base required for efficacy testing may be occasionally larger or may require longer patient observation than that suggested by this guideline.

Exceptions:

a. Instances where there is concern that the drug will cause late developing ADE's, or cause ADE's that increase in severity or frequency over time, would require a larger and/or longer-term safety data base. The concern could arise from:

(1) Data from animal studies;

(2) Clinical information from other agents with related chemical structures or from a related pharmacologic class;

(3) Pharmacokinetic or pharmacodynamic properties known to be associated with such ADE's.

b. Situations in which there is a need to quantitate the occurrence rate of an expected specific low frequency ADE will require a greater long-term data base. Examples would include situations where a specific serious ADE has been identified in similar drugs or where a serious event that could represent an alert event is observed in early clinical trials.

c. Larger safety data bases may be needed to make risk/benefit decisions in situations where the benefit from the drug is either: (1) small (e.g., symptomatic improvement in less serious medical conditions), (2) will be experienced by only a fraction of the treated patients (e.g., certain preventive therapies administered to healthy populations), or (3) is of uncertain magnitude (e.g., efficacy determination on a surrogate endpoint).

d. In situations where there is concern that a drug may add to an already significant background rate of morbidity or mortality, clinical trials may need to be designed with a sufficient number of patients to provide adequate statistical power to detect prespecified increases over the baseline morbidity or mortality.

e. In some cases, a smaller number of patients may be acceptable, for example, where the intended treatment population is small.

8. Filing for approval will usually be possible based on the data from patients treated through 6 months. Data on patients treated through 12 months should be submitted as soon as available and prior to approval in the United States and Japan but may be submitted after approval in the European Union. In the United States, the initial submission for those drugs designated as priority drugs should include the 12-month patient data.

Dated: February 23, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 95–4958 Filed 2–28–95; 8:45 am]

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federal register

Tuesday
December 13, 1994

Part II

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 201

Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling; Final Rule

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 92N-0165]

Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations governing the content and format on labeling for human prescription drug products. The final rule revises the current "Pediatric use" subsection of the professional labeling requirements for prescription drugs to provide for the inclusion of more complete information about the use of a drug in the pediatric population (ages birth to 16 years). The final rule, which applies to prescription drug products (including biological prescription drug products), recognizes several methods of establishing substantial evidence to support pediatric labeling claims, including relying, in certain cases, on studies carried out in adults. This final rule also requires that if there is not substantial evidence to support any pediatric use or use in a particular pediatric population, the labeling shall state this. Sponsors must reexamine existing data to determine whether the "Pediatric use" subsection of the labeling can be modified based on adequate and well-controlled studies in adults, and other information supporting pediatric use, and, if appropriate, submit a supplemental application to comply with new § 201.57(f)(9)(iv) by December 13, 1996. This action responds to concerns in FDA and elsewhere that current prescription drug labeling often does not contain adequate information about the use of drugs in the pediatric population. This action promotes safer and more effective use of prescription drugs in the pediatric population.

DATES: Effective January 12, 1995. The agency will accept "pediatric use" information based on revised § 201.57(f)(9) (21 CFR 201.57(f)(9)) after January 12, 1995. Sponsors must reexamine existing data, and, if appropriate, submit a supplemental application to comply with new § 201.57(f)(9)(iv) by December 13, 1996.

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SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of October 16, 1992 (57 FR 47423), FDA proposed to amend its regulations pertaining to the content and format of prescription drug labeling in § 201.57 by revising the current "Pediatric use" subsection (§ 201.57(f)(9)) to allow a broader basis for the inclusion of information about use of a drug in the pediatric population. The proposal would have allowed pediatric claims based not only on adequate and well-controlled studies in the pediatric population but also, in some cases, on such trials in adults. The proposed regulation described other data needed when pediatric claims are based on trials in adults and indicated specific labeling language and the location of various kinds of information.

FDA issued the current pediatric labeling requirements in 1979 (44 FR 37434, June 26, 1979). The current regulation, codified at § 201.57(f)(9), requires that specific pediatric indications, if any, be described under the "Indications and Usage" section of the labeling, with appropriate pediatric dosage provided under the "Dosage and Administration" section. The current regulation also requires that recommendations for pediatric use be based on substantial evidence derived from adequate and well-controlled studies in the pediatric population, unless that requirement is waived. If a drug's safety and effectiveness in the pediatric population cannot be established or if the drug's use in the pediatric population is associated with a specific hazard, the current regulation requires appropriate statements or details.

By establishing a "Pediatric use" subsection and describing its content and format, the 1979 regulation was intended to encourage drug labeling that would regularly provide adequate information about use of prescription drugs in pediatric patients. As stated in the preamble to the proposed rule on which this final rule is based, however, most prescription drug products still lack adequate information about their use in pediatric populations. For example, an informal survey done in 1990 by the American Academy of Pediatrics examined labeling of all new molecular entities approved between 1984 and 1989 and found that 80 percent had no information on pediatric use. Other surveys have shown that the labeling for many prescription drugs states that safety and effectiveness in children have not been established and contains no information on pediatric use, even for drugs that are commonly prescribed for pediatric patients.

FDA continues to be concerned that, without adequate information, practitioners may be reluctant to prescribe certain drugs for their pediatric patients, or may prescribe them inappropriately, choosing dosages, for instance, that are arbitrarily based on the child's age, body weight, or body surface area without specific information as to whether this is appropriate. As a result, pediatric patients may be exposed to an increased risk of adverse reactions, or decreased effectiveness of the drugs prescribed, or may be denied access to valuable therapeutic agents.

The continuing absence of pediatric use information in prescription drug labeling may be due in part to the impression, perhaps conveyed by the existing regulation, that pediatric claims must always be based on adequate and well-controlled studies conducted in the pediatric population. Given the many problems associated with the testing of drugs in the pediatric population (e.g., obtaining informed consent for tests not directly of benefit to the child, use of placebo controls in a vulnerable population), studies meeting this standard are often difficult to obtain. Existing FDA regulations do not, in fact, require that controlled trials always be conducted in the pediatric population to support a pediatric use. Under current § 201.57(f)(9), the need for such studies may be waived where other data can satisfy the requirements of law. The basis for granting such a waiver is not, however, clear in the existing regulation. Section 201.57(f)(9)(iv) of this final rule clarifies how the agency will determine that data from adequate and well-controlled studies with adult subjects can provide substantial evidence of effectiveness in the pediatric population.

In summary, this rule is intended to provide practitioners with more pediatric use information in the labeling of human prescription drug products so that practitioners will have more reliable information upon which to base a decision to prescribe a drug for use in their pediatric patients. The rule does this by encouraging manufacturers to provide more information on drug labels upon which practitioners can base their decisions. The rule does not, however, limit the manner in which a practitioner may prescribe an approved drug.

II. Highlights of the Final Rule

The final rule revises the current "Pediatric use" subsection of the professional labeling requirements for prescription drugs to provide for the inclusion of more comprehensive information about use of a drug in the pediatric population. Under the final rule, products may be labeled for pediatric use based on adequate and well-controlled studies in adults together with other information supporting pediatric use (e.g., pharmacokinetic data, safety data, pharmacodynamic data). Such reliance on studies in adults was possible under the waiver provision in the existing rule, but the waiver provision was not often used. Of course, products may also be labeled for pediatric use based on adequate and well-controlled studies in the pediatric population. The pediatric age group, birth to 16 years, includes pediatric age groups often called neonates, infants, children, and adolescents. In the final rule, because the term "children" can be interpreted as referring only to a particular subset of the pediatric population (ages 2 to 12 years), and to make clear that the provisions of this rule apply to the entire pediatric population, references to "children" in the proposed rule have been deleted and replaced by "pediatric population" or "pediatric patients."

The major provisions of the final rule are summarized as follows:

The final rule continues to permit a specific pediatric indication (i.e., an indication different from those approved in adults) supported by adequate and well-controlled studies in the appropriate pediatric population, to be described under the "Indications and Usage" section of the labeling, with the appropriate pediatric dosage given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection of the labeling must include any limitations on the pediatric indication, need for specific monitoring, specific hazards of the drug, differences between pediatric and adult responses to the drug, and other information related to the safe and effective use of the drug in pediatric patients.

If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they must be summarized in the "Pediatric use" subsection of the labeling and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage must be given under the "Dosage and Administration" section of the labeling. This subsection of the labeling must also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug.

A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted.

Where the requirements for a finding of substantial evidence to support a specific pediatric indication or a pediatric use statement have not been met for a particular pediatric subgroup, the "Pediatric use" subsection of the labeling must contain a statement that appropriately characterizes the limitation, such as "Safety and effectiveness in pediatric patients [below the age of (—) (years/months/weeks)] have not been established." If use of the drug is associated with a specific hazard in this pediatric subgroup, the "Pediatric use" subsection must contain information about this hazard, or, where appropriate, refer to a more complete description of the hazard in the "Contraindications" or "Warnings" section of the labeling.

Where the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, the "Pediatric use" subsection of the labeling must contain the following statement: "Safety and effectiveness in pediatric patients have not been established." If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the "Pediatric use" subsection must contain information about this hazard, or, where appropriate, refer to a more complete description of the hazard in the "Contraindications" or "Warnings" section of the labeling.

Any sponsor who believes that no "Pediatric use" subsection is appropriate or relevant to the labeling of its particular drug product must provide FDA with reasons justifying its omission, and may propose alternative statement(s).

Finally, recognizing the hazards that inactive ingredients can pose to the pediatric population, the final rule requires that prescription drug labeling contain statements about inactive ingredients that might be toxic to the neonate or other pediatric subgroup.

III. General Comments on the Proposed Rule

FDA received 11 comments on the proposed rule from prescription drug manufacturers, prescribers, professional societies, organizations with special interests in the pediatric population, the lay public, and others. Most supported the proposed labeling change, calling it "timely and important," "an important * * * step to facilitate the inclusion of information about use of drugs in children in the approved labeling," "a significant step toward the goal of including infants and children in the drug approval process," and a way "to fill the gap of information that currently exists in the area of appropriate drug usage in children."

One comment, for example, stated that providing pediatric use information in labeling will help health professionals reach rational drug therapy decisions for pediatric patients. The comment added "any information that can be used by pharmacists to assure rational drug therapy in special populations will be a positive addition to drug information. * * * Such labeling will enhance the likelihood of positive outcomes in pediatric patients."

However, some comments were less supportive, including one that stated: "While * * * [we] commend the FDA on its initiatives to improve information available to physicians and their pediatric patients regarding prescription drug use, we remain concerned that this approach will not measurably assist physicians."

Most comments also raised specific issues for consideration by the agency. These issues are described below.

A. Definition of "Pediatric"

1. Several comments suggested that age breakdowns within the pediatric population might be appropriate. The pediatric age range begins at birth, and may cover individuals as old as 18 years to 21 years, encompassing the subspecialties of neonatology and adolescent medicine. One comment suggested that the rule define "pediatric" as children under 12 years, because "it has been commonly accepted that ages 12 years to 18 years may be included without previous clinical work in that age group." The

comment also suggested that the rule state the age group when pharmacokinetic studies should be done in order to extrapolate the results from infancy through adolescence, or state whether the age range will be broken into subgroups with testing required for each. Another comment said that a definition of "pediatric" would have to consider drug metabolism, pharmacokinetics, and interaction with various organs and other body systems. The comment suggested that a system by which distinct classes of drugs are considered differently may be more logical and appropriate.

Another comment noted that pediatric patients are not homogeneous, and that age groups show significant differences in functional and physiological functions. The comment suggested that information from clinical studies be subdivided by age groups and their respective responses to drugs, suggesting age categories of premature infant, newborn, children under 2 years of age, children 2 years to 13 years, and adolescents 13 years to 18 years.

Another comment said that individuals 16 years to 18 years of age pose particular problems and suggested consultation with the American Academy of Pediatrics' Committee on Drugs to consider defining age categories or groups for pediatric labeling.

The "Pediatric use" subsection of labeling is where information about use of a drug in pediatric patients is located, and § 201.57(f)(9) describes in general terms the kind of information that should be included. The "Pediatric use" subsection does not attempt to resolve the many difficult issues related to use of drugs in this population. What appears in this subsection (e.g., age groups covered) will depend on the data available, and the ability to define results for specific subgroups. As a general matter, however, the agency offers the following guidance and useful breakdowns. The following age categories for the pediatric population are commonly distinguished, although the distinctions are inevitably arbitrary: (1) Birth up to 1 month (neonates), (2) 1 month up to 2 years of age (infants), (3) 2 years up to 12 years (children), and (4) 12 years up to 16 years (adolescents). Where possible, data should be analyzed by these groups, but it should not usually be necessary to establish a drug product's effectiveness in each group. It may, on the other hand, be important to have some pharmacokinetic information in each group, especially the younger age groups, to guide dosing and additional information, such as a specific study in neonates, to establish safety.

Although the agency has determined that the term "pediatric patients" refers to individuals from birth to 16 years of age, the agency recognizes that for some drugs, adult studies may be applicable to pediatric patients under the age of 16 years who have passed puberty; indeed, a primary purpose of this rule is to allow pediatric labeling based on adult studies, when appropriate. Although in many cases, additional pharmacokinetic and safety data may be needed to support pediatric use statements, in other cases, particularly for pediatric patients in the 12-to 16-year age group, there may be less additional data needed.

B. Applicability of the Rule to Biological Drug Products

2. One comment said that it was unclear whether the rule applies to biological drug products.

The rule (as well as § 201.57 in general) applies to biological drug products.

C. Pediatric Studies

3. One comment noted that about 80 percent of drug labeling currently contains language excluding use of the drug in pediatric patients or limiting use only to specific age groups. The comment asked FDA to encourage sponsors to include pediatric patients in their clinical studies when the drug is likely to be effective for an indication in this population.

As stated in the preamble to the proposed rule, FDA encourages sponsors to include pediatric patients in their clinical studies, and analyzes investigational new drug applications and new drug applications (NDA's) to determine whether studies in this population should be done before the drug is approved (57 FR 47423 at 47424). Under certain circumstances, the agency may require that clinical studies in the pediatric population be conducted before marketing approval (see response to comment number 4 in section III.C. of this document). If a drug is likely to be effective for pediatric use, the agency is making it clear that labeling for pediatric use may sometimes be based on adequate and well-controlled studies in adults, with additional pediatric data. FDA intends that this rule will call further attention to the need for creating and reviewing data on pediatric use.

4. One comment asked whether FDA intended to require a sponsor to submit information for a specific pediatric indication or use if there are available data suggesting that such an indication or use would be permitted under the regulation. The comment said that there may be "good reasons" why a sponsor might not wish to seek a pediatric indication or use for a drug even when available evidence would support such a use. For example, the drug's benefit/risk ratio in the pediatric population might be different from that in adults, or there might be sufficient and better alternative therapies available for the pediatric use. Additionally, the comment expressed concern that a drug that has been tested in adults may not provide a sufficient legal defense against a claim for injury of a child. The comment said that a sponsor should not be forced to assume or be placed in the position of having to defend such an action unless the sponsor believes the data in support of the pediatric use are sufficient, and that a sponsor should not be mandated or forced by the rule to seek a pediatric use if the sponsor, for whatever reason, does not wish to do so.

Another comment expressed concern that FDA might delay approval of products that have good existing available data for safety and efficacy in adults while acceptable pediatric information is developed.

This rule does not add a new requirement that sponsors carry out new pediatric studies, nor does it require that sponsors submit labeling with claims that are inadequately supported. New § 201.57(f)(9)(iv) provides that a pediatric use statement may be based on adequate and well-controlled studies in adults, provided that the course of the disease and the drug effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Sponsors are required to reexamine existing data to determine whether the "Pediatric use" subsection of the labeling can be modified based on adequate and well-controlled studies in adults, and other information supporting pediatric use, and, if safety and effectiveness for pediatric use have been demonstrated, submit a supplemental application to comply with new § 201.57(f)(9)(iv) by December 13, 1996. A sponsor who does not believe that the disease and drug effects are similar in the pediatric and adult populations, or who believes that use in pediatric patients is otherwise not adequately supported by data, should not propose revised labeling under this provision. Under new § 201.57(f)(9)(vi), the sponsor may propose labeling stating that safety and effectiveness in pediatric patients have not been established.

Additionally, under new § 201.57(f)(9)(vii), if the sponsor

believes that none of the statements described in paragraphs (f)(9)(ii) through (f)(9)(vi) of that section is appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose alternative statement(s). In response to such a proposal, FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate. Section 201.57(f)(9)(vii) has been modified to make this explicit.

Although this rule does not add new requirements for conducting pediatric studies, various provisions of the Federal Food, Drug, and Cosmetic Act (the act), the Public Health Service Act (the PHS act), and existing regulations authorize FDA to require such studies under certain circumstances.

Under section 505(k) of the act (21 U.S.C. 355(k)), FDA may require NDA holders to establish records and submit reports to the agency on data relating to clinical experience or other data or information in order to determine whether there may be grounds for revoking the NDA approval. Such a requirement may be established either through regulation or through an order regarding the NDA (21 U.S.C. 355(k)(1)).

Existing regulations require application holders to report to the agency adverse experiences occurring in the course of use of the product in professional practice, as well as during clinical investigations (21 CFR 312.32, 314.80). In addition, approved application holders must submit as part of the annual report a summary of significant new information that might affect the safety, effectiveness, or labeling of the product, as well as copies of unpublished and published reports of studies of the drug (21 CFR 314.81(b)(2)(i), (b)(2)(v), and (b)(2)(vi)). The report also must contain a description of the action the company has taken or intends to take because of the new information, such as submission of a supplement, addition of a warning, or initiation of a new study (21 CFR 314.81(b)(2)(i)).

Section 505(e) of the act specifies grounds on which the agency may withdraw or suspend approval of an NDA. If there is an imminent hazard to the public health, approval of the NDA may be suspended immediately by the Secretary of the Department of Health and Human Services. In addition to other circumstances, approval of an NDA is to be withdrawn if clinical experience or other data show that the product is unsafe or not shown to be safe under the conditions of use upon the basis of which the application was approved. Moreover, the approval may be withdrawn if the labeling is false or misleading and not corrected within a reasonable time after notice of the matter.

Under section 502(a) of the act (21 U.S.C. 352(a)), a drug is considered misbranded if its labeling is false or misleading. Section 201(n) of the act (21 U.S.C. 321(n)) makes it clear that the "misleading" determination is to be based not only on representations made or suggested in the labeling, but also on failure to reveal material facts. Material facts include those which concern consequences which may result from use of the product under the labeled conditions of use or under customary or usual conditions of use. These conditions of use may include off-label uses prescribed by practitioners for their patients.

In addition, drugs are considered misbranded under section 502(f) of the act if the labeling fails to bear adequate directions for use. FDA regulations define adequate directions for use as directions under which the lay person can use a drug safely and for the purposes for which it is intended (21 CFR 201.5). "Intended uses" are further defined in the regulations to include uses other than the ones on the labeling (21 CFR 201.128). If a manufacturer knows that a drug is used for an off-label use, the manufacturer may be required to provide adequate labeling for that use (21 CFR 201.128).

Prescription drugs for human use are exempt from the requirement to carry adequate directions for lay use under certain circumstances, if labeled with the prescription legend (21 CFR 201.100). Among the exemption criteria is the requirement that the drug carry adequate labeling for the prescriber, as authorized by an approved application, for the intended use. In summary, the drug product is misbranded if the intended use is not approved in an NDA.

Drug products are also misbranded, under section 502(f)(2) of the act, if the labeling does not carry adequate warnings against unsafe use. Such unsafe use may include use by pediatric patients where the use may be dangerous to their health, or unsafe dosage or methods or duration of administration in the pediatric population.

Biological drug products are approved under authority of section 351 of the PHS act (42 U.S.C. 262). This provision authorizes the promulgation of regulations designed to ensure the continued safety, purity, and potency of the products (42 U.S.C. 262(d)(1)). An approved product license application (PLA) may be revoked if the product does not conform to applicable requirements in the regulations or is not safe and effective for all of its intended uses or is misbranded with respect to any such use (21 CFR 601.5(b)(4) through (b)(6)). If there is a danger to health, the Commissioner may suspend the product license (21 CFR 601.6). Under section 351(b) of the PHS act, no one may falsely label a biological product. Biological drug products are also subject to the applicable drug provisions of the Federal Food, Drug, and Cosmetic Act, as previously discussed.

Moreover, the agency has stated that an application for marketing approval should contain data on a reasonable sample of the patients likely to be given a drug once it is marketed (58 FR 39406 at 39409, July 22, 1993). This conclusion, stated explicitly in a guideline on the need for data in both genders, applies equally to age subgroups, including pediatric and geriatric populations. FDA may refuse to approve an application that fails to contain sufficient information to determine whether the product can be safely and effectively used in populations likely to receive it. In addition, for an approved drug, in certain cases (e.g., where the drug is widely used, represents a potential hazard, or is therapeutically important in pediatric patients), FDA may require further studies in pediatric populations and appropriate labeling changes. As previously discussed, an already approved drug may be considered illegally marketed if adequate information on safe and effective use in pediatric patients is not obtained and included in the labeling.

The agency thus expects sponsors to seek supplemental claims for pediatric uses that are supported by adequate data. This does not imply, however, that a sponsor should seek a claim for a pediatric use if the benefits of that use do not outweigh its risks; the determination of whether to include a pediatric use statement must be based on clinical data, and other use information, not on a vague concern about liability.

5. One comment said that although the desire to use potentially relevant data in the "Pediatric use" subsection of the labeling was "understandable," such data should not take the place of adequate and well-designed controlled studies in the pediatric population, and that FDA ultimately may have to require such studies. The comment stated that FDA should require manufacturers to

fund research projects regarding drug safety and efficacy, including short-term and long-term side effects, in pediatric patients.

FDA agrees that clinical studies regarding a drug's safety and effectiveness in pediatric patients are desirable, and the agency encourages such studies in appropriate cases. As discussed in comment 4 in section III.C. of this document, the agency has the authority to require such studies under certain circumstances. In some cases, such studies may be required prior to approval where pediatric use is important and where the adult and pediatric diseases cannot be considered sufficiently similar. In other cases, the controlled trials in adults, with pharmacokinetic and other data as needed, may support valid pediatric labeling.

6. One comment stated that FDA should consider other alternatives to the rule, including a formal review process that collects and analyzes available safety and efficacy data on a drug's use in the pediatric population both before and after marketing approval, which, through committee review, could recommend further testing of the drug after it is marketed if specific pediatric safety or efficacy concerns are found.

FDA believes that the comment has misinterpreted the purpose of the rule. The rule describes the kind of data and information that can be included in labeling for the pediatric population. In general, it is the sponsor's responsibility to collect, on a continuing basis, available data on safety and efficacy, propose revised labeling, and carry out needed studies. In some circumstances, FDA has required pediatric studies prior to approval, elicited agreement by drug sponsors at the time of marketing approval to carry out additional pediatric studies after approval, or stimulated conduct of pediatric studies after approval. When appropriate, FDA makes use of its standing advisory committees to help decide whether and when pediatric studies are needed.

7. One comment stated that FDA should revise the rule to specify what data must be provided by manufacturers. The comment asked what number of pediatric patients would be sufficient to determine if there is a difference in age-related response, and how FDA will determine that all available information about the pediatric use of all available drugs has been included, including epidemiologic studies.

FDA declines to accept the comment's suggestion. The agency believes that specifying an exact number of pediatric patients to be studied would be impractical due to variations in the pediatric population and responses to different drugs. This is particularly true, given the various kinds of data that can be used under the rule to support pediatric labeling.

D. Drugs Currently Under Review

8. One comment suggested that drugs currently under development or under review by FDA should be given special consideration to avoid delays in development and approval associated with implementation of the rule.

FDA does not expect delays in review or approval as a result of this rule. FDA already examines available pediatric data under current labeling regulations. The principal change created by the revised regulation is the ability to rely on studies in adults to support pediatric efficacy in some situations.

E. Supplements for Drugs Already Approved

9. One comment suggested that FDA work with manufacturers of approved drugs to develop a method that allows the manufacturers to update their labeling in a quick and cost-effective manner. The comment also said that package inserts do not generally reflect current scientific literature because of the problems with current methods of updating labeling. The comment said that this had created situations where prescribers are making decisions on treatment modalities without the benefit of timely information.

FDA does not believe that changes in regulations are needed to allow timely updating of labeling. Under the current regulations, applicants can propose changes in their approved labeling. FDA normally reviews supplements subject to prior approval in the order received. Effectiveness supplements are rated as priority or standard and are subject to performance goals set in connection with the Prescription Drug User Fee Act of 1992.

10. One comment said that the filing and approval of pediatric labeling supplements from different sponsors on different timetables could mean that some labels for products considered to be substantially similar might be silent with regard to pediatric usage, while others might be detailed. The comment suggested that FDA and the American Academy of Pediatrics' Committee on Drugs could identify therapeutic classes to be relabeled first, so that FDA could review and approve pediatric use labeling for products from different companies and coordinate implementation of labeling changes for similar agents.

With respect to effectiveness claims, pharmacokinetics, and safety data, much information is drug specific and will be reviewed as it is submitted. Therefore, the agency is not adopting the comment's suggestions. The agency advises, however, that, in general, when a class of drug products is involved, FDA examines labeling as it applies to the class.

F. Impact on Industry

11. One comment claimed that the rule places NDA holders at a competitive disadvantage relative to abbreviated new drug application (ANDA) holders. The comment stated that the rule would give NDA holders the burden and responsibility for pediatric studies and literature searches, but not impose a similar burden and responsibility on ANDA holders.

FDA disagrees with the comment in part. The rule is directed to anyone marketing a prescription drug and is intended to encourage the inclusion of more complete information about use of a drug in the pediatric population and about hazards associated with this use. The rule permits a new basis for reference to pediatric uses, but it does not impose a new requirement to conduct studies in pediatric populations. To the extent that NDA holders have access to data not available to ANDA holders, they will have more data to examine and more likelihood of having a basis for proposing changes to the "Pediatric use" subsection of labeling. The agency believes this represents only a modest burden and, in any event, sees no other way to gain further pediatric information in labeling. ANDA holders cannot be required to examine data they do not possess. ANDA holders are not precluded from providing pediatric use data, and are expected to do so under this rule, if data are available. An ANDA applicant who believes new safety or effectiveness information should be added to a product's labeling should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.

G. Minor Editorial Changes

12. One comment said that labeling revisions that are editorial in nature and are used to reformat existing pediatric use labeling information to conform to the rule should be made in accordance with § 314.70(d) (21 CFR 314.70(d)) (changes described in the annual report). The comment said that this would also facilitate the agency's processing of minor changes.

FDA agrees with the comment. As stated in the preamble to the proposed rule, "[m]inor editorial changes may be made in accordance with § 314.70(d)" (57 FR 47423 at 47426). To comply with this rule, references to "children" in the "Pediatric use" subsection of the insert labeling of products already being marketed must be changed, where appropriate, to "pediatric population" or "pediatric patients." For products other than biological products, such changes are considered minor editorial changes.

As stated in the preamble to the proposed rule, for biological products, such changes are to be submitted in accordance with the procedures outlined in § 601.12 (21 CFR 601.12) (57 FR 47423 at 47426).

H. Format of Proposed Labeling

13. One comment said that it is impractical and impossible to list on the labeling all dosages and hazards for the pediatric population. The comment suggested placement of a general label on all adult prescription drugs stating that the medication should not be given to pediatric patients without a physician's instructions. The comment said that requiring overly complicated and lengthy information on labeling would discourage the prescribing of needed medications.

FDA believes that the comment misinterprets the proposed rule and the purpose of pediatric use labeling. The purpose of the rule is to encourage more pediatric use information in labeling and to provide practitioners with more information on pediatric use.

14. One comment said that for certain products, e.g., corticosteroids, where class labeling has been in effect, the agency will have to decide and communicate how the pediatric wording will be addressed.

In most cases, pediatric labeling will be drug specific. Where class labeling exists, FDA generally examines the labeling for those products as a whole.

IV. Specific Comments on the Proposed Rule

A. Section 201.57(f)(9)(i)

FDA, on its own initiative, has added a definition in § 201.57(f)(9)(i) to indicate that under paragraphs (f)(9)(ii) through (f)(9)(viii), the terms "pediatric population(s)" and "pediatric patient(s)" are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

B. Proposed § 201.57 (f)(9)(i) and (f)(9)(ii)

FDA received no comments on these provisions (renumbered as § 201.57(f)(9)(ii) and (f)(9)(iii)), and has finalized them without change.

C. Proposed § 201.57(f)(9)(iii)

Proposed § 201.57(f)(9)(iii) (renumbered as § 201.57(f)(9)(iv)) states, in part, that "FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drugs are sufficiently similar in children and adults to permit extrapolation from the adult data to children. The additional information supporting pediatric use must include data on the pharmacokinetics of the drug in children for determination of pediatric dosage. Other information, such as data from pharmacodynamic studies of the drug in children, controlled or uncontrolled studies confirming the safety or effectiveness of the drug in children, pertinent premarketing or postmarketing studies or experience, may be necessary to establish the applicability of the adult data to children."

15. One comment said FDA should revise proposed § 201.57(f)(9)(iii) to indicate that pharmacokinetic data are not mandatory in some situations. Another comment stated that pharmacokinetic data may not be the most appropriate way to determine pediatric dosing because the differences in metabolism or in distribution in pediatric patients may support dosing that will not necessarily be related to blood levels. Both comments stated that dosing for inhalation products should not be based on pharmacokinetics.

Another comment said that difficulties in obtaining informed consent, use of placebo controls, and obtaining adequate blood samples for pharmacokinetic analysis in pediatric patients are not serious impediments to performing studies necessary for appropriate pediatric labeling. The comment said there is a well-established ethical structure within which informed consent may be obtained and placebo controls used in the pediatric population, and that current technology requires only very small blood samples for measurement of most compounds. According to the comment, the primary impediments to doing adequate clinical trials in the pediatric population are the absence of a regulatory mandate and the existence of economic disincentives.

The agency recognizes that pharmacokinetic data are important sources of information, but may not always be the most appropriate method for determining pediatric dosing schedules and may be infeasible, unnecessary, or insufficient. Other types of data or experience may sometimes substitute for pharmacokinetic data, and other data or experience in the pediatric population may be needed in addition to pharmacokinetic data. The agency has modified the rule to state that the additional information supporting pediatric use must *ordinarily* include data on the pharmacokinetics of the drug in the pediatric population for determination of pediatric dosage.

As discussed in response to comment 4 in section III.C. of this document, this rule does not create a new requirement for pediatric studies, but the authority for requiring pediatric studies already exists. There are situations in which data on safe and effective use in pediatric patients may be necessary for approval or for continued marketing of a drug. Revised § 201.57(f)(9) does not create the requirement for pediatric studies, but is intended to encourage the inclusion of more comprehensive labeling about pediatric use by permitting use of adult data in establishing pediatric efficacy. Specifically, the rule allows the pediatric use statement to be based on adequate and well-controlled studies in adults when additional information exists to show that the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients to permit extrapolation from the adult efficacy data to pediatric populations.

FDA has, on its own initiative, amended proposed § 201.57(f)(9)(iii) to indicate that FDA's determination whether the effects of a drug are sufficiently similar in adults and pediatric patients will include an examination of the drug's beneficial and adverse effects. FDA has also amended § 201.57(f)(9)(iii) to make clear that other information besides pharmacokinetic data may be necessary not simply to "establish the applicability of the adult data to pediatric patients," but, more generally, "to show that the drug can be used safely and effectively in pediatric patients." Section 201.57(f)(9)(iii) has also been modified to remove any potential misimpression that uncontrolled studies could demonstrate effectiveness.

16. One comment questioned the rule's language about extrapolating adult data to pediatric patients. The comment said that the exact mechanism

by which many psychiatric drugs work is not known, so that, for these drug products, extrapolation between adult and pediatric populations may be inaccurate and potentially hazardous. The comment noted that randomized controlled studies of tricyclic antidepressants in pediatric patients have raised questions regarding efficacy, while safety issues have been raised based on noncontrolled data indicating a potential risk, which might not have been clear based on adult data, of sudden cardiac death in pediatric patients using tricyclics.

FDA agrees that extrapolation from adult experience is inappropriate, and thus unacceptable, in some cases. Extrapolation is not necessary under the rule, but is an alternative to the conduct of adequate and well-controlled studies in pediatric patients. In those cases where the pediatric use statement is based primarily on adequate and well-controlled studies in adults, additional information supporting pediatric use is usually needed, ordinarily including data on the pharmacokinetics of the drug in the pediatric population for determination of pediatric dosage. Other information, such as data from pharmacodynamic studies of the drug in pediatric patients, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in the pediatric population.

17. One comment said that the preamble to the final regulation should clarify that "other information" supporting pediatric use in proposed § 201.57(f)(9)(iii) need not be limited to data developed or sponsored by the NDA holder, but may include data such as reports of studies by academic researchers in peer-review journals that were prepared by persons who are not related to the NDA sponsor.

The agency believes that no change is needed in revised § 201.57(f)(9)(iv) because the section does not suggest that the data must have been developed or sponsored by the NDA holder.

D. Proposed § 201.57(f)(9)(iv)

FDA received no comments on this provision (renumbered as § 201.57(f)(9)(v)), and has finalized it without change.

E. Proposed § 201.57(f)(9)(v)

Proposed § 201.57(f)(9)(v) (renumbered as § 201.57(f)(9)(vi)) provides, in part, that "[i]f the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling shall contain the following statement: 'Safety and effectiveness in children have not been established.'"

18. One comment expressed concern that this provision may create disincentives for sponsors to develop better information on pediatric use of their drugs. The comment suggested that FDA require mandatory phased-in safety testing and appropriate clinical studies of pharmaceuticals in the pediatric population. Alternatively, the comment recommended that FDA and manufacturers work to develop agreements whereby the manufacturer consents to carry out additional postapproval pediatric studies.

FDA believes that the comment suggests actions beyond the scope of this rule. FDA encourages pediatric testing, and, as discussed in comment 4 in section III.C. of this document, has the authority to require pediatric studies. In some cases, FDA will require pediatric studies for approval or continued marketing. This rule, however, does not add new requirements for pediatric studies, but rather describes the kind of data that can be used to support labeling claims.

F. Proposed § 201.57(f)(9)(vi)

Proposed § 201.57(f)(9)(vi) (renumbered as § 201.57(f)(9)(vii)) provides "[i]f the sponsor believes that none of the statements described in paragraphs (f)(9)(i) through (f)(9)(v) (renumbered as (f)(9)(ii) through (f)(9)(vi)) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement."

19. One comment asserted that the proposal did not adequately address the problem of a large number of drugs that have been approved and marketed for years without pediatric usage information in their labeling, which are widely used in pediatric patients and for which there is substantial published literature regarding their pediatric use. The comment noted that proposed § 201.57(f)(9)(vi) would impose on the sponsor the responsibility for providing information that would promote the safe and effective use of prescription drugs in pediatric patients and noted that the sponsor may have complex reasons for not necessarily wanting to include pediatric information in the labeling. The comment recommended that the final rule include a mechanism that would allow summary information from authoritative published literature to be added to the labeling of currently marketed drugs so this information would be available to the pediatric prescriber. It suggested that the rule should provide an option permitting "recognized authoritative medical experts or groups of experts" to provide information to support pediatric information in the labeling in lieu of the sponsor.

Another comment urged the agency to provide for the incorporation of supplemental indications into drug labeling based solely on information submitted by persons other than the sponsor. The comment said that changes should be made based on studies reported in peer-reviewed medical literature, rather than relying on submissions by the sponsor. The comment stated that this was necessary to make the labeling of certain drugs, particularly anticancer agents, conform to the current state of medical knowledge. The comment noted that FDA restricts promotion of off-label uses, and third-party payers often take the position that agents that have no labeled indication for treatment of cancers in pediatric patients are experimental and therefore nonreimbursable, even though they may be safe and effective.

The sponsor is primarily responsible for bringing forth evidence to support labeling changes. A third party could, however, provide evidence to persuade the agency to direct the sponsor to submit a labeling supplement. A study need not have been conducted by or on behalf of the sponsor in order to support a labeling change. The evidence to support labeling should continue to be of the type and quality that would ordinarily support labeling statements. Published literature on pediatric use may contribute to this evidence, and authoritative groups may suggest approaches, but the views of authoritative groups do not themselves represent sufficient evidence of effectiveness. With respect to the comment concerning reimbursements, the agency advises that reimbursements to patients are beyond the scope of the rule and FDA authority. However, FDA agrees with the underlying concern that appropriate indications be on the label so that practitioners understand how best to prescribe the drug for the patient's medical benefit.

G. Proposed § 201.57(f)(9)(vii)

Proposed § 201.57(f)(9)(vii) (renumbered as § 201.57(f)(9)(viii)) states "[i]f the drug product contains one or more excipients that present an increased risk of toxic effects to

neonates or other pediatric subgroups, a special note of this risk, generally in the 'Contraindications,' 'Warnings,' or 'Precautions' section, shall be made."

. Four comments expressed concern about this proposed requirement. One comment said that the data relating to the toxicity of excipients, including preservatives, are inconclusive, making the requirement inappropriate. The comment stated that FDA should encourage collection and analysis of data to enable specific determinations on the use of excipients and preservatives.

Another comment asked FDA to clarify whether the proposed requirement that labeling contain statements about excipients that present an increased risk of adverse effects to the neonate or other pediatric subgroups was intended to reflect published literature or to be based on studies designed to show whether an increased risk exists. It added that it was not clear how or by whom a determination of increased risk would be established. The comment suggested that the final rule state that a sponsor can rely on existing information and is not required to conduct additional studies. The comment also suggested that, if additional studies were necessary, animal data be used rather than requiring clinical studies in neonates. It suggested that a standardized list could be developed jointly by industry and FDA.

A third comment suggested that a requirement that any labeling identify any increased risk of toxic effects to neonates or other pediatric groups should not be interpreted as establishing a requirement that sponsors conduct toxicology or other studies to identify or quantify such risks. The comment also stated that the preamble to the final regulation should state whether the increased risk of toxic effects is limited to those established by human data or experience, or would also include those based on animal or in vitro models.

A fourth comment noted that ANDA holders may use excipients different from those used by the reference listed drug. The comment suggested that ANDA holders should be required to provide specific information regarding excipients used.

The final rule requires the labeling for a drug product containing one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups to note such risks in the "Contraindications," "Warnings," or "Precautions" section of the labeling. If toxicity data for the inactive ingredient(s) do not exist or are inconclusive, revised § 201.57(f)(9)(viii) would not require the labeling to contain a statement about an increased risk to neonates or other pediatric subgroups. However, in such cases, FDA encourages applicants to collect and analyze data on inactive ingredients and preservatives that could represent a pediatric risk. These data may include human data, animal data, or data derived from in vitro models.

FDA also notes that current regulations already require ANDA applicants whose inactive ingredients differ from those used in the reference listed drug to identify and characterize the inactive ingredients in a proposed drug product and to provide information demonstrating that such inactive ingredients do not affect the safety of the proposed drug product (see 21 CFR 314.94(a)(9)). Given these provisions, there is no reason to believe that the inactive ingredients used in a generic drug product are any less safe than those in the reference listed drug.

The agency has determined that, for the purposes of this final rule, the terms "excipient" and "inactive ingredient" have the same meaning. However, because the agency generally uses the term "inactive ingredient," the agency has, on its own initiative, amended proposed § 201.57(f)(9)(vii) to refer to "inactive ingredients" instead of "excipients."

V. Legal Authority

FDA's revision to the "Pediatric use" subsection of prescription drug labeling is authorized by the Federal Food, Drug, and Cosmetic Act (the act) and by the Public Health Service Act (the PHS act). Section 502(a) of the act prohibits false or misleading labeling of drugs, including, under section 201(n) of the act, failure to reveal material facts relating to potential consequences under customary conditions of use.

Section 502(f) of the act requires drug labeling to have adequate directions for use and adequate warnings against use by the pediatric population where its use may be dangerous to health, as well as adequate warnings against unsafe dosage or methods or duration of administration, as are necessary to protect users.

Section 502(j) of the act prohibits use of drugs that are dangerous to health when used in the manner suggested in their labeling. Drug products that do not meet the requirements of any paragraph of section 502 of the act are deemed to be misbranded.

In addition to the misbranding provisions, the premarket approval provisions of the act authorize FDA to require that prescription drug labeling provide the practitioner with adequate information to permit safe and effective use of the drug product. Under section 505 of the act, FDA will approve an NDA only if the drug is shown to be both safe and effective for its intended use under the conditions set forth in the drug's labeling. Section 701(a) of the act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the act.

Under § 201.100(d) (21 CFR 201.100(d)) of FDA's labeling regulations, prescription drug products must bear labeling that contains adequate information under which licensed practitioners can use the drug safely for their intended uses. Section 201.57 describes specific categories of information, including information for drug use in selected subgroups of the general population, which must be present to meet the requirements of § 201.100.

In addition, under 21 CFR 314.125, FDA will not approve an NDA unless, among other things, there is adequate safety and effectiveness information for the labeled uses and the product labeling complies with the requirements of part 201 (21 CFR part 201).

Section 351 of the PHS act provides legal authority for the agency to regulate the labeling and shipment of biological products. Licenses for biological products are to be issued only upon a showing that they meet standards "designed to insure the continued safety, purity, and potency of such products" prescribed in regulations (42 U.S.C. 262(d)). The "potency" of a biological product includes its effectiveness (21 CFR 600.3(s)). Section 351(b) of the PHS act prohibits false labeling of a biological product. FDA's regulations in part 201 apply to all prescription drug products, including biological products.

A drug product that is not in compliance with § 201.57(f)(9) would be considered misbranded and an unapproved new drug under the act. A noncomplying product that is a biological product would, in addition, be considered falsely labeled and an unlicensed biological product under the PHS act.

VI. Implementation

The primary purpose of the proposed rule was to revise the existing pediatric labeling requirements by expanding the basis on which information about use of a drug in the pediatric population may be included. The proposed rule would have required sponsors to comply with the pediatric use provisions 1 year after the date of publication of a final rule in the Federal Register.

21. Several comments said that the proposed 1-year implementation period was too short. The comments claimed that extrapolating and reviewing data would be time consuming and that the agency would be unable to approve pediatric use labeling within 1 year. The comments suggested that the agency cooperate with industry to establish a 3–year implementation schedule, only require sponsors to submit revised labeling in 1 year, or make the rule effective in 2 years.

The agency has carefully considered the comments and has revised the implementation schedule for the final rule. The agency will accept pediatric use information based on revised § 201.57(f)(9) after January 12, 1995.

Sponsors have a continuing obligation to maintain labeling that is truthful and comprehensive in accordance with § 201.57, including § 201.57(f)(9). Section 201.57(f)(9) requires labeling to contain at least one of the statements under § 201.57(f)(9)(ii) through (f)(9)(vi), or to propose an alternative statement under § 201.57(f)(9)(vii). The statement must accurately describe available data.

Sponsors must, therefore, reexamine existing data to determine whether the "Pediatric use" subsection of the labeling can be modified based on adequate and well-controlled studies in adults and other information supporting pediatric use, and, if appropriate, submit a supplemental application to comply with new § 201.57(f)(9)(iv) by December 13, 1996. A sponsor who does not believe that the disease and drug effects are similar in the pediatric and adult populations, or who believes that use in pediatric patients is otherwise not adequately supported by data, should not propose revised labeling under new § 201.57(f)(9)(iv), and need not inform the agency of this conclusion.

Therefore, FDA expects sponsors to examine available information and update pediatric labeling for their products, if appropriate. Sponsors should also examine data on the extent and nature of use of their products in pediatric patients. If FDA concludes that a particular drug is widely used, represents a safety hazard, or is therapeutically important in the pediatric population, and the drug sponsor has not submitted any pediatric use information, then the agency may require that the sponsor develop and/or submit pediatric use information.

If FDA has made a specific request for the submission of pediatric use information because of expected or identified pediatric use, and the sponsor fails to provide such information, the agency may consider the product to be a misbranded drug under section 502 of the act, or a falsely labeled biological product under section 351 of the PHS Act, as well as an unapproved new drug or unlicensed biological product. (See 21 U.S.C. 355 and 42 U.S.C. 262).

Under the final rule, any new or revised pediatric indications, or statements on pediatric indications, or statements on pediatric use under the provisions of § 201.57(f)(9)(ii) through (f)(9)(iv) would require FDA approval of a supplemental application in accordance with § 314.70(b) or § 601.12. Other changes to proposed § 201.57(f)(9)(ii) through (f)(9)(iv) to add or strengthen precautions, contraindications, warnings, or adverse reactions or to add or strengthen dosage and administration instructions to increase a product's safety (for products other than biological products) could be put into effect at the time a supplement covering the change is submitted to FDA in accordance with § 314.70(c). Minor editorial changes to products other than biological products may be made in accordance with § 314.70(d).

To comply with this rule, references to "children" in the "Pediatric use" subsection of the insert labeling of products already being marketed must be changed, where appropriate, to "Pediatric population" or "pediatric patients." The agency advises that after January 12, 1995, such changes must be made, no later than the first time that labeling is sent to the printers or ordered for reprinting to replenish old stocks of labeling. Such changes for products other than biological products are considered minor editorial changes and may be submitted in an annual report in accordance with § 314.70(d).

Any new or revised statement under § 201.57(f)(9)(viii) regarding inactive ingredients that may be toxic to the neonate or other pediatric subgroup should be made in accordance with the provisions of § 314.70(c) or § 601.12 (21 CFR 601.12), as appropriate.

All supplements containing pediatric use information and their mailing covers should be plainly marked "Pediatric supplements."

For those products subject to section 351 of the PHS act, labeling changes should be made in accordance with § 601.12. Persons who have questions regarding such changes and need guidance on whether a supplement is necessary should contact one of the following three divisions as appropriate: Office of Therapeutics Research and Review, Division of Application Review and Policy (HFM–585), 301–594–5109; Office of Vaccine Research and Review, Division of Vaccine and Related Product Applications (HFM–475), 301–594–2090; or Office of Blood Research and Review, Division of Blood Applications (HFM–370), 301–594–2012; at the following address: Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852.

22. One comment suggested that the rule would have a substantial economic impact, particularly if the agency adheres to the proposed 1-year implementation period. The comment said that there are cost factors arising from the extensive resources required to reevaluate the available clinical study data and literature to extrapolate adult safety data to the pediatric age group or groups. The comment noted that drug studies in pediatric patients have additional costs not experienced with the adult population, and may, in some cases, require inpatient studies. The comment also claimed that encouraging pediatric studies prior to approval or as a Phase 4 commitment could lengthen the development process, slow drug approval, and thereby have an additional economic impact.

The agency has considered the comment and has revised the implementation schedule for this final rule. The implementation schedule is discussed in section VI. of this document.

The agency stresses that this rule does not require sponsors to conduct pediatric studies. The authority to require studies is found in the act and regulations already promulgated. Rather, this rule recognizes alternative methods of establishing substantial evidence to support pediatric labeling claims. Where a finding of substantial evidence to support a pediatric indication or a pediatric use statement has not been met for a specific subgroup or for any pediatric population, the sponsor must instead indicate that no data are available. If a sponsor believes that a pediatric use statement would be inappropriate or irrelevant to the labeling of a particular drug, it must provide a reason for omitting the statement. This rule does not affect any determination by the agency that pediatric studies are needed before or after approval for a new drug.

VII. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the principles set out in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the final rule does not impose additional requirements for sponsors to conduct pediatric studies, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 201 is amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 508, 510, 512, 530–542, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg–360ss, 371, 374, 379e); secs. 215, 301, 351, 361 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 264).

2. Section 201.57 is amended by revising paragraph (f)(9) to read as follows:

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

* * * * *

(f) * * *

(9) Pediatric use:

(i) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (f)(9)(ii) through (f)(9)(viii) of this section, the terms "pediatric population(s)" and "pediatric patient(s)" are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(ii) If there is a specific pediatric indication (i.e., an indication different from those approved for adults) that is supported by adequate and well-controlled studies in the pediatric population, it shall be described under the "Indications and Usage" section of the labeling, and appropriate pediatric dosage information shall be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection shall cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. Data summarized in this subsection of the labeling should be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or "Clinical Studies" section. As appropriate, this information shall also be contained in the "Contraindications," "Warnings," and elsewhere in the "Precautions" sections.

(iii) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they shall be summarized in the "Pediatric use" subsection of the labeling and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage shall be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection of the labeling shall also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information shall also be contained in the "Contraindications," "Warnings," and elsewhere in the "Precautions" sections.

(iv) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the "Pediatric use" subsection of the labeling shall contain either the following statement, or a reasonable alternative: "The safety and effectiveness of (*drug name*) have been established in the age groups — to — (*note any limitations, e.g.*, no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (*drug name*) in these age groups is supported by evidence from adequate and well-controlled studies of (*drug name*) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population)." Data summarized in the preceding prescribed statement in this subsection of the labeling shall be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or the "Clinical Studies" section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the "Clinical Pharmacology" section. Pediatric dosing instructions shall be included in the "Dosage and Administration" section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients shall be cited briefly in the "Pediatric use" subsection and, as appropriate, in the "Contraindications," "Warnings," "Precautions," and "Dosage and Administration" sections.

(v) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the

"Pediatric use" subsection of the labeling shall contain an appropriate statement such as "Safety and effectiveness in pediatric patients below the age of (—) have not been established." If use of the drug in this pediatric population is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.

(vi) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling shall contain the following statement: "Safety and effectiveness in pediatric patients have not been established." If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.

(vii) If the sponsor believes that none of the statements described in paragraphs (f)(9)(ii) through (f)(9)(vi) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

(viii) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk shall be made, generally in the "Contraindications," "Warnings," or "Precautions" section.

* * * * *

Dated: November 15, 1994.

David A. Kessler,

Commissioner of Food and Drugs.

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