SAFETY REVIEW

A. METHODS

This safety database covers all adverse treatment emergent events (ie. not present at baseline) that occurred on treatment or within 56 days of the last day of study treatment. The COSTART system was used for classification of adverse avents (AEs). A 60 day followup was used to determine if the AE resolved off therapy. Since experience has shown that AE ascertainment can differ qualitatively in placebo controlled settings compared to active controlled ones, AE comparisons are given separately for the placebo controlled group (US301 and MN301) and the active controlled group (MN302). When denominators are sufficient, cumulative incidences are used because they more accurately reflect the ongoing risk faced by the patient and clinician with ongoing use of an agent.

B. PATIENT ACCOUNTABILITY

SAFETY DATABASE: The total safety database of 1339 LEF patients consists of a "controlled study" and a "uncontrolled study" cohort:

a) Controlled studies: US301, MN301, and MN302 are detailed in the Efficacy Section of this review. Also included in this cohort is study YU203, a phase 2, dose finding study of six months duration, randomizing 402 RA to PLC, 5mg/d, 10mg/d, or 25mg/d of LEF. Total LEF exposure in the controlled study cohort is 1116 RA patients. Patient experiences in ***alternate therapy*** in trials US301 and MN301 are NOT included in this n = 1339 database; this would entail double counting. The exception is rare or serious Aes, which are reported in the sponsor's Integrated Summary of Safety. These patients' treatment assignments are still blinded. Some of these further data will be available in the 120 day update.

b) Uncontrolled studies: One hundred forty-nine patients were exposed in phase 2 studies, including 34 at 5mg/d, 35 at 10 mg/d, and 31 at 25mg/d, plus 24 at 100mg/wk and 25 at 200mg/wk. There are also 74 patients who had been on placebo in YU203 who were then open-label extended (in trial YU205) on LEF. Thus, the total LEF exposure in the uncontrolled study cohort is 223 LEF patients.

Cutoff dates for the safety database are July 1997, for adverse reactions in general, September 1997 for rare adverse events, and December 1997 for serious

adverse events and deaths.

OTHER INDICATIONS / ONGOING STUDIES: Data from two completed studies are separately included in the safety analysis: Protocol 201PS - a double-blind, placebo-controlled study (arms: 5mg/d, 10mg/d, 25mg/d, and PLC) of 96 patients with psoriasis vulgaris, and Protocol 101TA - a single dose study of 7 patients with chronic renal graft rejection on concomitant cyclosporine and prednisone. A number of studies are ongoing, including Protocols MN302, MN305, US301 (yr 2), 3006, F01 (MTX/LEF co-use), 102PS, 2001 (systemic lupus erythematosis), and 2012 (Wegener's granulomatosis patients, in remission). Overall adverse events from these studies are not included in this analysis because the trials are still blinded. However, serious adverse events occuring up to July 1, 1997 are included.

C. EXPOSURE

The global safety database is shown below, by exposure over time:

Table 4 Exposure Over Time

	≤4 Weeks (≤ 28 days)		4-12 Weeks (29-84 days)		12-24 Weeks (85-168 days)		24-36 Weeks (169-252 days)		36-52 Weeks (253-336 days)		>52 Weeks (>336 days)	
	N	%	N	%	N	%	N	%	N	%	N	%
LEF	46	3.5	106	8.0	161	12.2	87	6.6	86	6.5	838	63.3
PL	5	1.6	31	10.0	184	59.4	43	13.9	9	2.9	38	12.3
MTX	19	2.8	33	4.9	75	11.1	32	4.7	20	3.0	497	73.5
SSZ	14	10.8	15	11.5	25	19.2	5	3.8	48	36.9	23	17.7

REF: Appendix Table 14.1, 14.2 (placebo).

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ON ORIGINAL

D. OVERALL SAFETY PROFILE

The two following tables represent the strightforward approach to the global safety profile. First is the overall summary of adverse events.

Table 7 Overall Summary of Adverse Events

	LEF		PL		MTX		SSZ	
	N	%	N	%	N	%	N	%
Total Number of Subjects	1339	100.0	210	100.0	680	100.0	133	100.0
Subjects w/ 1 or more AE	1117	83.4	174	82.9	632	92.9	121	91.0
Total Number of AEs	5419	NA	746	NA	3274	NA	502	NA
Subjects w/ 1 or more Drug-Related AE	801	59.8	108	51.4	474	69.7	98	73.7
Subjects Reducing Dose due to AE	45	4.0 n=1116	0	0	96	14.1	9	6.8
Subjects Discontinuing due to AE	207	15.5	15	7.1	91	13.4	30	22.6
Subjects w/ 1 or more SAE	294	22.0	22	10.5	149	21.9	22	16.5
Total Number of SAEs	377	NA	25	NA	202	NA	33	NA
Subjects w/ 1 or more Drug-Related SAE	65	4.9	7	3.3	43	6.3	11	8.3

REF: Appendix Tables 15, 44.1, 44.3, 47.1, 47.3, 50.1, 50.3, 52.1, 52.3, 54.1 and 54.3.

Secondly, is a table of COSTART termed adverse events occurring either (1) a frequency of at least 1% in the total LEF group (n = 1339), or (2) a frequency for LEF greater than for PLC in the placebo-controlled group (LEF: n = 315. PLC: n = 210).

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Table 8 Adverse Events with Frequency of 1% or Greater in all LEF Group and Frequency in LEF Group in Controlled Studies Equal to or Greater than Placebo

	All LEF TX'D RA		Placebo-Controlled Studies MN301 and US301								Active Control Study MN302			
			LEF		PL		MN301/3 SSZ		US301 MTX		MN302 MTX		LEF	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
	1339	100	315	100	210	100	133	100.0	182	100.0	498	100	501	100
Body as a Whole														
Abdominal Pain	74	5.5	16	5.1	8	3.8	5	3.8	14	7.7	19	3.8	29	5.8
Back Pain	66	4.9	20	6.3	7	3.3	5	3.8	16	8.8	34	6.8	38	7.6
Accidental Injury	65	4.9	22	7.0	11	5.2	4	3.0	20	11.0	34	6.8	32	6.4
Asthenia	43	3.2	20	6.3	8	3.8	7	5.3	10	5.5	16	3.2	13	2.6
Flu Syndrome	32	2.4	11	3.5	5	2.4	0	0.0	13	7.1	0	0.0	0	0.0
Pain	26	1.9	12	3.8	5	2.4	2	1.5	9	4.9	2	0.4	4	0.8
Infection	23	1.7	4	1.3	2	1.0	3	2.3	7	3.8	8	1.6	10	2.0
Allergic Reaction	20	1.5	15	4.8	5	2.4	0	0.0	10	5.5	9	1.8	5	1.0
Cardiovascular System														
Hypertension	138	10.3	28	8.9	9	4.3	5	3.8	5	2.7	20	4.0	49	9.8
Chest Pain	22	1.6	12	3.8	5	2.4	3	2.3	8	4.4	9	1.8	7	1.4
Tachycardia	20	1.5	3	1.0	2	1.0	0	0.0	2	1.1	1	0.2	10	2.0
Gastrointestinal System														
Diarrhea	227	17.0	84	26.7	25	11.9	13	9.8	35	19.2	50	10.0	111	22.2
Nausea	124	9.3	41	13.0	23	11.0	25	18.8	33	18.1	90	18.1	64	12.8
Dyspepsia	66	4.9	32	10.2	21	10.0	12	9.0	24	13.2	35	7.0	29	5.8
LFT Abnormal	65	4.9	32	10.2	5	2.4	5	3.8	19	10.4	84	16.9	29	5.8
GI Pain/Abd Pain	61	4.6	18	5.7	9	4.3	9	6.8	15	8.2	38	7.6	40	8.0
Vomiting	38	2.8	16	5.1	9	4.3	5	3.0	5	2.7	17	3.4	16	3.2
Anorexia	34	2.5	9	2.9	5	2.4	7	5.3	3	1.6	15	3.0	13	2.6
Flatulence	16	1.2	9	2.9	2	1.0	3	2.3	6	3.3	6	1.2	5	1.0
Cholelithiasis	15	1.1	3	1.0	0	0.0	1	0.8	0	0.0	3	0.6	3	0.6
Oral														
Mouth Ulcer	33	2.5	15	4.8	8	3.8	4	3.0	18	9.9	28	5.6	17	3.4
Tooth Disorder	24	1.8	9	2.9	4	1.9	1	0.8	5	2.7	20	4.0	7	1.4
Salivary Gland	19	1.4	3	1.0	0	0.0	1	0.8	0	0.0	4	0.8	5	1.0
Stomatitis	15	1.1	4	1.3	0	0.0	0	0.0	1	0.5	9	1.8	9	1.8
Hemic & Lymphatic System														
Leukopenia*	38	2.8	7	2.2	0	0.0	3	2.3	2	1.1	13	2.6	22	4.4
Metabolic & Nutritional Disorders														
Weight Loss	47	3.5	7	2.2	1	0.5	2	1.5	0	0.0	9	1.8	9	1.8
Hypokalemia	16	1.2	10	3.2	2	1.0	1	0.8	1	0.5	1	0.2	4	0.8
Musculo-Skeletal System														
Joint Disorder	54	4.0	8	2.5	4	1.9	3	2.3	3	1.6	28	5.6	39	7.8
Tenosynovitis	36	2.7	7	2.2	0	0.0	1	0.8	4	2.2	5	1.0	24	4.8
Myalgia	18	1.3	8	2.5	4	1.9	4	3.0	7	3.8	6	1.2	9	1.8
Arthralgia	17	1.3	11	3.5	7	3.3	0	0.0	16	8.8	1	0.2	3	0.6
Leg Cramps	16	1.2	11	3.5	5	2.4	3	2.3	10	5.5	12	2.4	5	1.0

Table 8 Adverse Events with Frequency of 1% or Greater in all LEF Group and Frequency in LEF Group in Controlled Studies Equal to or Greater than Placebo

	All LEF TX'D RA		Placebo-Controlled Studies MN301 and US301								Active Control Study MN302			
			LEF		PL		MN301/3 SS2		US301 MTX		MN302 MTX		LEF	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
	1339	100	315	100	210	100	133	100.0	182	100.0	498	100	501	100
Central Nervous System														
Headache	91	6.8	42	13.3	24	11.4	16	12.0	38	20.9	39	7.8	48	9.6
Dizziness	56	4.2	16	5.1	7	3.3	8	6.0	9	4.9	31	6.2	35	7.0
Paresthesia	29	2.2	9	2.9	3	1.4	1	0.8	4	2.2	14	2.8	18	3.6
Vertigo	23	1.7	4	1.3	2	1.0	5	3.8	0	0.0	9	1.8	7	1.4
Respiratory System														
Resp. Infection	202	15.1	66	21.0	43	20.5	27	20.3	58	31.9	122	24.5	133	26.5
Bronchitis	87	6.5	16	5.1	4	1.9	5	3.8	12	6.6	34	6.8	40	8.0
Pharyngitis	41	3.1	6	1.9	3	1.4	2	1.5	1	0.5	13	2.6	14	2.8
Rhinitis	32	2.4	15	4.8	5	2.4	5	3.8	5	2.7	10	2.0	12	2.4
Pneumonia	29	2.2	10	3.2	0	0.0	0	0.0	2	1.1	11	2.2	11	2.2
Sinusitis	26	1.9	15	4.8	10	4.8	0	0.0	18	9.9	7	1.4	7	1.4
Dyspnea	18	1.3	8	2.5	2	1.0	5	3.8	9	4.9	10	2.0	8	1.6
Skin														
Rash	132	9.9	39	12.4	14	6.7	14	10.5	16	8.8	48	9.6	54	10.8
Alopecia	130	9.7	28	8.9	3	1.4	8	6.0	11	6.0	49	9.8	81	16.2
Pruritis	57	4.3	15	4.8	4	1.9	4	3.0	4	2.2	10	2.0	29	5.8
Dry Skin	28	2.1	10	3.2	5	2.4	2	1.5	0	0.0	6	1.2	17	3.4
Eczema	25	1.9	4	1.3	1	0.5	1	0.8	1	0.5	9	1.8	17	3.4
Rash, Macpap	24	1.8	9	2.9	2	1.0	4	3.0	2	1.1	10	2.0	8	1.6
Skin Disorder	24	1.8	9	2.9	2	1.0	4	3.0	0	0.0	13	2.6	7	1.4
Herpes Simplex	18	1.3	4	1.3	1	0.5	3	2.3	10	5.5	12	2.4	11	2.2
Herpes Zoster	16	1.2	1	0.3	0	0.0	2	1.5	2	1.1	9	1.8	8	1.6
Acne	13	1.0	4	1.3	2	1.0	2	1.5	3	1.6	5	1.0	5	1.0
Special Senses														
Conjunctivitis	21	1.6	9	2.9	2	1.0	4	3.0	1	0.5	17	3.4	6	1.2
Urogenital System														
Cystitis	18	1.3	6	1.9	1	0.5	2	1.5	2	1.1	8	1.6	9	1.8
Dysuria	17	1.3	6	1.9	4	1.9	1	0.8	1	0.5	2	0.4	5	1.0
Increased Frequency	16	1.2	6	1.9	4	1.9	0	0.0	2	1.1	0	0.0	6	1.2

REF: Appendix Tables 44.1 and 44.3; US301 Study Report Table 241; MN302 Study Report Table 88.

• Not based on WBC count of <2.0 G/l.

Another perspective on the overall safety profile -- acutally on the overall safety/efficacy profile -- is obtained by simply enumerating the number of patients undergoing dose reductions for adverse reactions, on the one hand, versus, the number undergoing dose increases for inefficacy. These data are shown below:

Table 5 Summary of Study Medication Dose Modifications								
	LEF		PL		MTX		SSZ	
	N	%	N	%	N	%	N	%
Dose Decrease	45	4.0	3	1.4	96	14.1	9	6.8
Dose Increase	335*	49	81*	68.6*	343**	50.4	NA	NA

REF: Appendix Tables 15 and 16.
* Intended, not real, dose increase (MTX dummy increased).
**Real dose increase.

E. POTENTIAL CONFOUNDING FACTORS

To ascribe drug attribution in an RA trial often requires a judgment incorporating demographics and cotherapy. The standard data in this regard are summarized below.

Table 2 Summary of Demographics and Other Baseline Characteristics								
Characteristic	LEF		PL		MTX		SSZ	
Controlled Studies (US301, MN301, MN302, MN303, YU203)								
	N (1116)	% (100)	N (312)	% (100)	N (680)	% (100)	N (133)	% (100)
Age								
Mean	55.54	NA	55.25	NA	56.59	NA	58.88	NA
SD	11.44	NA	11.02	NA	11.23	NA	11.39	NA
Range	20-79	NA	23-83	NA	19-85	NA	25-79	NA
<65 yrs old	838	75.1	254	81.4	495	72.8	82	61.7
≥ 65 yrs old	278	24.9	58	18.6	185	27.2	51	38.3
Gender								
Male	272	24.4	82	26.3	188	27.6	41	30.8
Female	844	75.6	230	73.7	492	72.4	92	69.2
Race								
Caucasian	1071	96.0	287	92.3	653	96.0	124	93.2
Other	45	4.0	24	7.7	27	4.0	9	6.8
Duration of RA prior to TX								
Mean	6.03	NA	7.1	NA	4.49	NA	7.38	NA
SD	6.49	NA	7.24	NA	5.27	NA	9.99	NA
Range								
≤2 yrs	375	33.6	98	31.5	288	42.4	56	42.1
>2-10 yrs	545	48.9	128	41.2	337	49.6	40	30.1
Over 10 yrs	195	17.5	85	27.3	55	8.1	37	27.8
No Prior DMARD	358	32.1	115	36.9	245	36.0	68	51.1
Conmed Use								
NSAID	938	84.1	255	81.7	558	82.1	104	78.2
Corticosteroids	663	56.7	148	47.4	419	61.6	61	45.9
Both	519	46.5	121	38.8	345	50.7	47	35.3

F. DEATHS, WITHDRAWALS FOR ADVERSE EVENTS, SERIOUS ADVERSE EVENTS

DEATHS: There were 46 deaths in all studies, 8 in phase 2, 38 in phase 3, and 18 in extension protocols. Twenty were receiving LEF, 20 MTX, 2 PLC, and 1 occurred prior to treatment. A list of these 46 patients with demographics, cause of death, and comorbidities are shown in a table in the appendix, followed by individual narratives for patients on LEF.

WITHDRAWAL FOR ADVERSE EVENTS: Two-hundred-seven of 1339 on LEF (15.5%, 18.1% in PLC controlled studies) withdrew because of an adverse event, compared with 13.4% on MTX, 22.6% on SSZ, and 7.1% on PLC.

OTHER SERIOUS ADVERSE EVENTS: Overall, serious adverse events (SAEs) occurred in 22% on LEF in all studies, and 16% on LEF in PLC-controlled studies, compared to 11% on PLC. Serious adverse events were seen in 26.8% on LEF compared to 21.9% on MTX, and in 26.3% on LEF compared to 16.5% on SSZ. The frequency of SAEs attributed to the drug in phase 3 trials were 2.9% on LEF, 6.3% on MTX, 8.3% on SSZ, and 3.3% on PLC. SAEs ascertainment was greater in Europe because several events there typically lead to hospitalization, while in the U.S. they would be treated on an outpatient basis.

G. SELECTED TOPICS

HYPERTENSION

Hypertension was reported as an adverse event (and independently assessed and verified for all occurrences to be a SBP$\geq$160 and/or DBP$\geq$90) at an overall rate of 8.9% in the LEF group, 2.7% for MTX, 3.8% for SSZ, and 4.3% in PLC. New onset hypertension occurred at the following rates:

	crude rate	rate/1000 pt-yr exposure
LEF	13/816 = 1.6%	0.6/1000 pt-yrs
MTX	5/680 = 0.7%	0.5/1000 pt-yrs
SSZ	0/133 = 0%	0/1000 pt-yrs
PLC	1/210 = 0.5%	0.4/1000 pt-yrs

The analysis of hypertension reported as an AE is shown in the table below, and a by-patient tabulation of the 77 LEF cases is given in the appendix (p6, 6/24/98 correspondence):

Table 9 Analysis of Subjects with Hypertension as Adverse Event

	US301						MN302				MN301			
Subject Category	LEF		PL		MTX		LEF		MTX		LEF		SSZ	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total Subjects	182	100	118	100	182	100	501	100	498	100	133	100	133	100
Hypertension reported as adverse event	20	11.0	6	5.1	5	2.7	49	9.8	20	4.0	8	6.0	5	3.8
Total with hypertension at baseline	15	8.2	6	5.1	2	1.1	40	8.0	18	3.6	8	6.0	5	3.8
Diagnosis of hypertension at BL	8	4.4	3	2.5	0	0.0	16	3.2	6	1.2	3	2.3	4	3.0
Blood pressure at baseline/screening							35	7.0	17	3.4	8	6.0	5	3.8
Sys.≥160 mmHg	4	2.2	1	0.8	1	0.5	20	4.0	13	2.6	5	3.8	3	2.3
Dias.≥90 mmHg	8	4.4	3	2.5	2	1.1	34	6.8	16	3.2	8	6.0	5	3.8
New-onset hypertension	5	2.7	0	0.0	3	1.6	9	1.8	2	0.4	0	0.0	0	0.0
Sys.≥160 mmHg (at ≥2 visits)	3	1.6	0	0.0	0	0.0	5	1.0	1	0.2	0	0.0	0	0.0
Dias.≥90 mmHg (at ≥2 visits)	5	2.7	0	0.0	1	0.5	9	1.8	1	0.2	0	0.0	0	0.0
Concomitant NSAIDs	5	2.7	0	0.0	3	1.6	8	1.6	2	0.4	0	0.0	0	0.0
Concomitant steroids	3	1.6	0	0.0	2	1.1	6	1.2	2	0.4	0	0.0	0	0.0

REF: Appendix Tables 393 and 394; US301 Study Report, p 151.

The trials had, by chance, more patients on LEF with baseline hypertension than did MTX, SSZ, or PLC. Analysis of the mean change in SBP and DBP for patients ***normotensive at baseline*** showed the following:

		US301	MN301	MN302
change in SBP (mmHg)	LEF	2.2	5.6	5.5
	PLC	5.0	2.9	2.1
	MTX	1.9		
	SSZ		2.7	
change in DBP (mmHg)	LEF	1.9	3.8	4.6
	PLC	1.2	3.9	0.7
	MTX	1.3		
	SSZ		2.0	

Thus, the trials showed changes of BP in the range of 1 to 5mmHg in all groups including PLC, without any obvious consistent drug effects discernable. Over 80% of the patients in these trials were on concomitant NSAIDs, which can induce approximately the same BP change. It is difficult to attribute causation to LEF regarding this AE; some even feel that hypertension, per se, is a comorbidity in RA.

Regardless of attribution, it is important to assess the responsiveness of those becoming hypertensive on treatment to standard anti-hypertensive therapy. The clinical features of these patients are shown in the table below:

Table 18 Summary of Patients with Hypertension as an Adverse Event

	LEF all RA Studies		Placebo-Controlled Studies: US301 & MN301								Active Control Study: MN302			
			LEF		PL		MN301/3 SSZ		US301 MTX		MTX		LEF	
Criteria	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total Patients	1339		315		210		133		182		498		501	
Occurrence	138	10.3	28	8.9	9	4.3	5	3.8	5	2.7	20	4.0	49	9.8
AE	136	10.2	26	8.3	9	4.3	5	3.8	5	2.7	19	3.8	49	9.8
SAE	4	0.3	2	0.6	1	0.5	0	0.0	0	0.0	1	0.2	2	0.4
Study Treatment														
Discontinued	5	0.4	2	0.6	2	1.0	0	0.0	0	0.0	1	0.2	3	0.6
Duration														
Mean	73.49		75.84		70.42		26.08		27.67		50.83		77.76	
2 days or less	9	0.7	1	0.3	0	0.0	0	0.0	0	0.0	2	0.4	4	0.8
3 to 7 days	5	0.4	1	0.3	0	0.0	1	0.8	0	0.0	1	0.2	3	0.6
8 to 28 days	9	0.7	1	0.3	1	0.5	0	0.0	2	1.1	1	0.2	5	1.0
Greater than 28 days	49	3.7	13	4.1	3	1.4	3	2.3	1	0.5	2	0.4	17	3.4
Severity														
Mild	71	5.3	14	4.4	3	1.4	2	1.5	4	2.2	6	1.2	20	4.0
Moderate	56	4.2	11	3.5	5	2.4	3	2.3	1	0.5	13	2.6	25	5.0
Severe	10	0.7	3	1.0	1	0.5	0	0.0	0	0.0	1	0.2	4	0.8
Relatedness														
Not Related	75	5.6	17	5.4	5	2.4	2	1.5	4	2.2	11	2.2	28	5.6
Possibly Related	60	4.5	10	3.2	4	1.9	3	2.3	1	0.5	9	1.8	21	4.2
Probably Related	1	0.1	1	0.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Treatment														
None	2	0.1	2	0.6	1	0.5	0	0.0	1	0.5	0	0.0	0	0.0
Drugs/Therapy	135	10.1	25	7.9	7	3.3	5	3.8	2	1.1	20	4.0	49	9.8
Outcome														
Resolved	76	5.7	15	4.8	4	1.9	4	3.0	3	1.6	6	1.2	27	5.4
Resolved w/Sequelae	1	0.1	0	0.0	1	0.5	1	0.8	0	0.0	0	0.0	1	0.2
Continuing	60	4.5	13	4.1	4	1.9	0	0.0	2	1.1	14	2.8	21	4.2
Cumulative Incidence (KMA%)														
1 month or less		--		3.6		1.0		0.8		0.0		1.0		1.2
3 months or less		--		5.4		3.1		4.4		0.0		1.9		3.4
6 months or less		--		6.9		5.5		4.4		0.6		2.6		6.2
9 months or less		--		10.0		5.5		4.4		3.9		3.3		8.5
12 months or less		--		12.8		5.5		4.4		3.9		4.1		11.4

REF: Appendix Tables 54.1, 54.3, 63.1, 63.2 and 379; US301 Study Report p. 152; MN302 Study Report Tables 100, 101 and 123.

The AEs were generally mild or moderate. Of 137 patients with hypertension as an AE on LEF, 135 were treated with drugs, and followup showed 76 "resolved" (meaning followup visits did not show a persistence of hypertension), one resolved with sequalae, and 60 were continuing on antihypertensive treatment without indication that their BP was more difficult to control than expected.

SERIOUS HYPERTENSION EVENTS: A case of hypertensive encephalopathy on LEF is described in the appendix.

LIVER FUNCTION ABNORMALITIES

Monthly liver function test (LFT) monitoring was done in all three pivotal trials but the protocols differed significantly regarding (1) use of folate, known to protect against MTX toxicity, and (2) use of investigator discretion (MN302) versus protocol mandated (US301) dosage manipulations for LFT abnormalities. These protocol differences are noted because they affect the nature of the LFT data and their interpretation regarding conclusions about the utility of monthly monitoring of liver enzymes in patients on LEF versus MTX.

US301
monitoring: biwkly x 6, then monthly
nature of action: mandatory
action: confirm w/in 72hr
If >2, <3 ULN: decrease (both arms); repeat w/in 7-14d; if >3 ULN discontinue; if <3 ULN continue til next visit LFT check; if >2 ULN discontinue; if <2 ULN may continue.
If >3: discontinue. If confirmatory value <3 but >2, follow above rule.
concomitant folate with MTX: 100%
ETOH: advised against
protocol LFT exclusion definition: "Persistently abnormal LFTs - >2 serial elevations >1.2Xnml for AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin; or persistently abnormal albumin."

MN301
monitoring: biwkly x 4, then monthly
nature of action: discretionary
action: per investigator
protocol LFT exculsion definition: "Patients with active liver disease or previous liver disease which has not resolved completely, defined by serum levels of either SGOT, SGPT, alkaline phosphatase or bilirubin 2Xnml."

MN302 monitoring: biwkly x 4, then monthly
nature of action: discretionary
action: per investigator
concomitant folate with MTX: not mandated (used approx. 10%)
ETOH: no warning
protocol LFT exclusion definition: "Active liver disease or previous liver disease which has not resolved completely by serum levels of SGPT 2Xnml."

Number and percentage of patients -- all patients versus patients with basline normal LFTs -- showing various LFT elevations are displayed below. These data are all inclusive of the n = 1339 safety database, regardless of drug attribution.

Table 34 Marked Laboratory Abnormalities: Liver Function Tests

		LEF all RA Studies		Placebo-Controlled Studies: US301 & MN301								Active Control Study: MN302			
				LEF		PL		MN301/3 SSZ		US301 MTX		MTX		LEF	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Parameter	Criteria	1339		315		210		133		182		498		501	
SGOT	≥1.2xULN to <2xULN	215	16.1	33	10.5	9	4.3	14	10.5	14	7.7	113	22.9	66	13.3
	≥2xULN to <3xULN	81	6.1	14	4.5	3	1.4	--	--	12	6.6	42	8.5	14	2.8
	≥3xULN to <8xULN	19	1.4	4	1.3	2	1.0	5	3.8	1	0.6	30	6.1	7	1.4
	≥8xULN	5	0.4	2	0.6	--	--	--	--	--	--	2	0.4	1	0.2
SGPT	≥1.2xULN to <2xULN	222	16.7	61	19.4	20	9.5	13	9.8	20	11.0	89	18.1	85	17.1
	≥2xULN to <3xULN	131	9.8	15	4.8	--	--	11	8.3	12	6.6	75	15.2	28	5.6
	≥3xULN to <8xULN	42	3.2	11	3.5	3	1.4	1	0.8	6	3.3	85	17.2	19	3.8
	≥8xULN	6	0.5	2	0.6	1	0.5	2	1.5	--	--	11	2.2	1	0.2
Alk Phos	≥3xULN	13	1.0	0	0.0	0	0.0	3	2.3	0	0.0	1	0.2	7	1.4
Total bilirubin	≥30.8 umol/l	8	0.6	3	1.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.4
LDH	>400 U/l	56	4.5	12	3.8	7	3.3	12	9.0	0	0.0	5	1.0	5	1.0
Albumin	<25 g/l	11	1.4	4	1.3	1	0.5	1	0.8	0	0.0	2	0.4	6	1.2
Albumin	25 to 30 g/l	140	17.7	49	16.0	31	15.0	5	4.0	15	8.3	33	6.9	89	18.4
Subjects with Normal LFT Values at Baseline															
SGOT	>1.2 to <2ULN			34	10.8	8	3.8	13	9.8	13	7.1	112	22.5	59	11.8
	≥2 to <3ULN			12	3.8	3	1.4	--	--	11	6.0	36	7.2	12	2.4
	≥3ULN			6	1.9	2	1.0	5	3.8	1	0.5	29	5.8	7	1.4
SGPT	>1.2 to <2ULN			54	17.1	18	8.6	14	10.5	20	11.0	84	16.9	72	14.4
	≥2 to <3ULN			13	4.1	--	--	7	5.3	12	6.6	74	14.9	22	4.4
	≥3ULN			10	3.2	4	1.9	2	1.5	5	2.7	83	16.7	13	2.6
Alk Phos	≥3xULN			0	0.0	0	0.0	2	1.5	0	0.0	0	0.0	3	0.6

REF: Appendix Tables 75.1, 77.1, 77.3, 79 and 395 to 403

A composite display of LFT abnormalities by percent elevation is given below:

Table 35 Liver Function Test Abnormalities (Percent Above Indicated Limit)

	LEF			MTX		Placebo		SSZ
	MN301	MN302	US301	MN302	US301	MN301	US301	MN301
SGOT								
>1.2	10.5	15.6	20.9	35.5	13.7	4.3	7.6	12.8
>2	2.3	3.8	8.2	13.1	6.6	1.1	3.4	3.8
>3	1.5	1.4	2.2	5.8	0.5	0	1.7	3.8
SGPT								
>1.2	18.8	21.4	28.6	48.4	20.3	12.0	9.3	14.3
>2	2.3	7.0	11.0	31.5	9.3	1.1	2.5	6.0
>3	1.5	2.6	4.4	16.7	2.7	1.1	2.5	1.5
Alk Phos								
>1.2	8.3	6.6	5.5	5.4	2.2	1.1	3.4	5.3
>2	0.8	1.0	1.1	0.6	0	0	0	2.3
>3	0	0.6	0	0	0	0	0	1.5

REF: Appenix Tables 395 to 403.

The frequency of reversal of LFT abnormalities by drug is shown in the four tables below:

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Subjects with Normal SGPT at Baseline and > 1.2 x ULN during Treatment

Category	Leflunomide (N=176)		Placebo (N=118)		Methotrexate (N=179)	
	N	%	N	%	N	%
Subjects in cohort	48	27.3	10	8.5	37	20.7
Subjects with concomitant NSAIDs	38	21.6	3	2.5	23	12.8
Discontinued due to LFT abnormalities	11	6.3	2	1.7	7	3.9
Remained ≤ 2xULN on treatment	30	17.0	7	5.9	20	11.2
Reverted to ≤ 1.2xULN	42	23.8	9	6.8	29	15.6
At endpoint, with dose reduction	0	—	0	—	1	0.6
At endpoint, without dose reduction	32	18.2	6	5.1	22	12.3
After endpoint	10	5.7	3	2.5	6	3.4
>1.2xULN at endpoint and follow-up	6	3.4	1	0.8	8	4.5
>1.2xULN at endpoint and on NSAIDs	13	7.4	2	1.7	8	4.5

Subjects with Normal SGOT at Baseline and > 1.2 x ULN during Treatment

Category	Leflunomide (N=176)		Placebo (N=118)		Methotrexate (N=179)	
	N	%	N	%	N	%
Subjects in cohort	33	18.2	9	7.6	25	14.0
Subjects with concomitant NSAIDs	24	13.3	4	3.4	16	8.9
Discontinued due to LFT abnormalities	8	4.4	2	1.7	7	3.9
Remained ≤ 2xULN on treatment	20	11.0	5	4.2	13	7.3
Reverted to ≤ 1.2xULN	31	17.1	8	6.8	22	12.3
At endpoint, with dose reduction	0	—	0	—	0	—
At endpoint, without dose reduction	25	13.8	5	4.2	19	10.6
After discontinuation due to LFT	6	3.3	3	2.5	3	1.7
>1.2xULN at endpoint and follow-up	2	1.1	1	0.8	3	1.7
>1.2xULN at endpoint and on NSAIDs	6	3.3	2	1.7	4	2.2

Subjects with Normal SGPT at Baseline and > 3 x ULN during Treatment

Category	Leflunomide (N=176)		Placebo (N=118)		Methotrexate (N=179)	
	N	%	N	%	N	%
Subjects in cohort	8	4.5	3	2.5	4	2.2
Subjects with concomitant NSAIDs	5	2.8	2	1.7	2	1.1
Discontinued due to LFT abnormalities	6	3.4	2	1.7	2	1.1
Reverted to ≤ 1.2xULN	7	4.0	3	2.5	4	2.2
At endpoint, with dose reduction	0	—	0	—	0	—
At endpoint, without dose reduction	2	1.1	1	0.8	2	1.1
After endpoint	5	2.8	2	1.7	2	1.1
>1.2xULN at endpoint and follow-up	1	0.6	0	—	0	—
>1.2xULN at endpoint and on NSAIDs	3	1.7	1	0.8	1	0.6

Subjects with Normal SGOT at Baseline and > 3 x ULN during Treatment

Category	Leflunomide (N=176)		Placebo (N=118)		Methotrexate (N=179)	
	N	%	N	%	N	%
Subjects in cohort	4	2.2	2	1.7	1	0.6
Subjects with concomitant NSAIDs	3	1.7	2	1.7	0	—
Discontinued due to LFT abnormalities	3	1.7	1	0.8	1	0.6
Reverted to ≤ 1.2xULN	4	2.2	2	1.7	1	0.6
At endpoint, with dose reduction	0	—	0	—	0	—
At endpoint, without dose reduction	1	0.6	1	0.8	0	
After endpoint	3	1.7	1	0.8	1	0.6
>1.2xULN at endpoint and follow-up	0	—	0	—	0	—
>1.2xULN at endpoint and on NSAIDs	2	1.1	1	0.8	0	—

The frequency of reversal of LFT elevations by treatment is shown below.

Table 36	Frequency of Reversal of LFT Elevation: Leflunomide											
	MN301				MN302				US301			
	N/tot	%	rd	d/c	N/tot	%	rd	d/c	N/tot	%	rd	d/c
SGOT												
1.2-2	10/11	91.0	1	1	55/59	93.2	2	7	23/23	100.0	1	4
>2-3	1/1	100.0	0	0	12/12	100.0	2	2	11/11	100.0	0	5
3+	2/2	100.0	0	2	4/7	57.1	0	1	4/4	100.0	0	3
SGPT												
1.2-2	19/22	86.4	0	3	71/72	98.6	5	5	31/32	96.9	0	6
>2-3	1/1	100.0	0	0	19/22	86.4	1	3	10/12	83.3	0	2
3+	2/2	100.0	1	1	9/13	69.2	2	2	7/8	87.5	0	5
Alk Phos												
1.2-2	7/10	70.0	0	2	21/28	75.0	0	3	7/8	87.5	0	3

REF: Appendix Tables 395 to 403.
%=% reversed; rd=dose reduced; d/c=treatment discontinued;

Table 37	Frequency of Reversal of LFT Elevation: Methotrexate											
	MN301				MN302				US301			
	N/tot	%	rd	d/c	N/tot	%	rd	d/c	N/tot	%	rd	d/c
SGOT												
1.2-2					102/112	91.1	10	10	11/13	84.6	0	1
>2-3					36/36	100.0	8	9	10/11	91.0	0	5
3+					29/29	100.0	7	6	1/1	100.0	0	1
SGPT												
1.2-2					79/84	94.0	4	10	16/20	80.0	1	0
>2-3					61/74	82.4	12	8	9	75.0	0	4
3+					73/83	88.0	18	23	5/5	100.0	0	3
Alk Phos												
1.2-2					23/24	95.8	3	4	3/4	75.0	0	0

REF: Appendix Tables 395 to 403.
%=% reversed; rd=dose reduced; d/c=treatment discontinued.

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Table 39	Frequency of Reversal of LFT Elevation: Sulfasalazine											
	MN301				MN302				US301			
	N/tot	%	rd	d/c	N/tot	%	rd	d/c	N/tot	%	rd	d/c
SGOT												
1.2-2	11/12	91.7	1	3								
>2-3	0/0	-	0	0								
3+	4/5	80.0	0	3								
SGPT												
1.2-2	9/11	81.8	0	1								
>2-3	5/6	83.3	2	1								
3+	1/2	50.0	0	1								
Alk Phos												
1.2-2	3/4	75.0	0	1								

REF: Appendix Tables 395 to 403.
%=% reversed; rd=dose reduced; d/c=treatment discontinued;

Table 38	Frequency of Reversal of LFT Elevation: Placebo											
	MN301				MN302				US301			
	N/tot	%	rd	d/c	N/tot	%	rd	d/c	N/tot	%	rd	d/c
SGOT												
1.2-2	3/3	100.0	0	1					4/5	80.0	0	1
>2-3	1/1	100.0	0	0					2/2	100.0	0	2
3+	0/0	-	0	0					2/2	100.0	0	1
SGPT												
1.2-2	9/10	90.0	0	1					7/8	87.5	0	3
>2-3	0/0	-	0	0					0/0	-	0	0
3+	1/1	100.0	0	1					3/3	100.0	0	2
Alk Phos												
1.2-2	1/1	100.0	0	0					3/4	75.0	0	1

REF: Appendix Tables 395 to 403.
%=% reversed; rd=dose reduced; d/c=treatment discontinued.

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The eight cases of LEF SGOT/SGPT elevation > 3 x ULN are shown below:

Table 40 Reversibility of SGOT/SGPT Values >3xULN							
			Reversed to <1.2xULN				
Patient Number	SGOT >3	SGPT >3	SGOT	SGPT	Dose Reduction	D/C Rx	Reversed When
301-6-9	Yes	Yes	Yes	Yes	No	No	
301-11-2	No	Yes	Yes	Yes	No	Yes	2 mos
301-19-2	Yes	Yes	Yes	Yes	No	No	
301-29-6	Yes	Yes	Yes	Yes	No	Yes	3 mos
301-36-2	No	Yes	Yes	Yes	No	Yes	3 mos
301-36-6	Yes	Yes	Yes	No	No	Yes	
301-42-1	No	Yes	Yes	Yes	No	Yes	2 wks
301-42-16	No	Yes	Yes	Yes	No	Yes	2 wks

SERIOUS LFT ABNORMALITIES: The following are case reports:

LEF: pt 11008 - 62yo alcoholic 3mo into therapy hospitalized with sepsis, GI bleed, and biopsy proven GI vasculitis during which LFTs rose 3-4x ULN. LEF was stopped, and she was treated with cholestyramine with eventual complete recovery. Further information, including liver biopsy report, follows:

> Subject US301-11-008, a 62 year old female, with a history of alcoholism, hepatitis and elevated LFTs, was hospitalized for septicemia after a dental abscess unsuccessfully treated with antibiotics at week 10 after receiving leflunomide. While in the hospital the subject underwent a liver biopsy. LFTs were normal until two weeks prior to hospitalization Biopsy revealed fatty changes which affected two thirds of the hepatocytes. Except for mild xanthomatous changes, most of the portal areas appeared normal. Kupffer cells appeared mildly hyperplastic and a few macrophages had accumulated around occasional fatty liver cells. There were no features of a primary inflammatory process or demonstrated fibrosis. The biopsy was read as advanced fatty changes. (Roegnik Grade II)

LEF: pt 29006 - 68yo 8mo into therapy developed marked increase in LFTs. LEF was discontinued and cholesytramine administered without effect. The patient's sustained release niacin, along with other all other medications, were then discontinued, followed by resolution of her LFTs. The investigator assessed the event as related to LEF, but an independent hepatologist implicated the niacin as the culprit hepatotoxin. Further details follow:

Subject 29006 was a 68 year old female who, after 36 weeks of leflunomide intake, had a severe reversible increase in SGPT (39 x ULN) and SGOT (24 x ULN).

Leflunomide was discontinued and cholestyramine was administered. After stopping leflunomide and receiving treatment with cholestyramine, LFTs continued to rise for another 3 weeks. The subject was advised to stop concomitant sustained release niacin and lovastatin and the LFTs remained elevated for another 3 weeks. Transaminases started to decrease at week 30 and normalized by week 44. Bilirubin and PT remained normal throughout and the subject remained asymptomatic.

An ultrasound at week 35 revealed liver size to be at the upper limits of normal with fatty infiltration as well as incidental probable hemangioma. The subject denied alcohol intake. The subject had a history of cholesterolemia for which she had taken lovastatin since 1989 and niacin since 1995. She increased the niacin dose in December of 1995. Sustained release niacin has been reported to cause hepatitis. The Investigator assessed the event as related to leflunomide.

While it was concluded that the event must be attributed to leflunomide administration, the time course for normalization of transaminases after stopping sustained release niacin is suggestive, but not diagnostic, for the contribution of niacin.

LEF: pt 10155:-

Subject 10155 was a 55 year old female who, after 9 weeks of leflunomide intake had nausea, vomiting, headache, malaise, nasal congestion, and sweating without jaundice or change in urine color. She was seen at the emergency room and laboratory tests showed severe increases in SGPT (80 x ULN), SGOT (41 x ULN) and alkaline phosphatase (3 x ULN). Leflunomide was discontinued. However, cholestyramine and/or charcoal were not administered. She was asked to discontinue diclofenac and prednisone and after a week, the enzymes started to decrease and by week 11 they were slightly elevated prior to normalizing. Bilirubin and PT remained normal throughout. The subject had a history of infection with hepatitis B and denied history of alcohol intake. She also decreased her prednisone on her own without tapering and or advice from the treating physician. Following resolution of all LFT elevations, she was rechallenged with diclofenac and prednisone without any increase in LFTs. The Investigator assessed the event as related to leflunomide. A liver ultrasound did not reveal gallstones or obstruction.

MTX: pt 07019 - 25yo 8mo into therapy developed SGPT of 163 and SGOT of 99. MTX was stopped with normalization within 3wk.

MTX: pt 17017 - 35yo 3mo into therapy developed SGPT of 199 and SGOT of 59, which after MTX discontinuation, normalized after 2wk.

PLC: pt 16010 - 43yo developed >5x ULN LFT abnormalities on day17 which recurred on rechallenge on day 33. PLC was discontinue and cholestyramine given. LFTs normalized and remained normal on crossover LEF therapy.

LIVER BIOPSY: Use of the ACR liver biopsy criteria for monitoring MTX therapy in trial US301 study lead to the biopsy of one patient LEF, revealing Roegnik Grade IIIA histology, and one on MTX, showing Roegnik Grade I. These patients are described below:

Subject US301-16-001 received methotrexate and underwent liver biopsy after 50 weeks of treatment. Biopsy revealed moderate fatty changes and "hepatocellular necrosis consistent with methotrexate administration." The histological changes were consistent with those seen in patients receiving repeated administration of small therapeutic does of certain hepatotoxic drugs such as methotrexate. The degree of fatty change may have been partially due to this patient's underlying diagnosis of diabetes mellitus (Roegnik Grade I).

Subject US301-14-010, a 72 year old female with a history of cholelithiasis and persistently elevated LFTs, underwent liver biopsy after 106 weeks of leflunomide treatment. Biopsy revealed the architecture of the liver to be preserved. There were no fatty changes and the portal triads did not have an increased number of lymphoid cells. The biopsy was read as mild fibrosis grade III. (Roegnik Grade IIIA)

The three patients in the combination LEF and MTX study (Study F01) who met criteria for liver biopsy are described below:

Subject F01-55-007, a 50 year old female with a history of persistent elevated SGOT and SGPT underwent a liver biopsy after 58 weeks of combination therapy with leflunomide and methotrexate. Biopsy revealed normal hepatic parenchyma with anisonuclocytosis. Iron stains were negative for stainable iron. PAS stain was negative for cytoplasmic inclusions. No fibrosis was noted. (Roegnik Grade I)

Subject F01-56-001, a 60 year old female with a history of persistently elevated SGOT and SGPT underwent a liver biopsy after 60 weeks of combination therapy with leflunomide and methotrexate. Biopsy revealed mild steatosis, patchy periportal chronic active inflammation with focal piecemeal necrosis. Focal hepatocyte necrosis and increased portal fibrosis with early septa formation were present without an increase in stainable iron or dilated centrilobular sinusoids or central vein. (Roegnik Grade IIIA).

Subject F01-55-004, a 67 year old male with history of persistent elevated SGOT and SGPT underwent a liver biopsy after 60 weeks of combination therapy with leflunomide and methotrexate. The biopsy revealed moderate steatosis of the liver. Mild periportal fibrosis and mononuclear infiltrate in portal areas was consistent with methotrexate effect. No cirrhosis was demonstrated. (Roegnik grad IIIA).

CONCLUSION: The overall assessment of these data is that LEF and MTX are similar enough to justify using the same monitoring for both. The MTX label suggests liver enzyme monitoring every 1-2 months. A separate conclusion is that these data seem to strongly support the utility of folate for LFT protection in MTX therapy.

HEMATOLOGIC ABNORMALITIES

There were no significant problems identified in this area. The patients demonstrating a change from normal at baseline to abnormal are shown in the "shift table" below. "Normal" here was WBC = 4000, PMN = 1960, platelet = 130,000. Patients captured with this table showed a change from a baseline normal value to either an endpoint abnormal value or two abnormal values within the trial. A "shift table" showing clinically important hematologic abnormalities is shown next. Here even just one qualifying abnormal laboratory is sufficient to "capture" the patient:

Table 23 Shifts from Normal at Baseline to Abnormal at Endpoint or at Two Evaluations: Hematology Parameters													
		Placebo Controlled Studies: US301 & MN301								Active Control Study: MN302			
		LEF		PL		MN301/3 SSZ		US301 MTX		MTX		LEF	
		N	%	N	%	N	%	N	%	N	%	N	%
Parameter	Criteria	315		210				182		499			
Hb	<LLN	34	10.8	29	13.8	24	18.0	19	10	77	15.5	63	12.6
Hct	<LLN	26	8.3	33	15.7	15	11.3	18	9.9	63	12.7	68	13.6
WBC	<LLN	46	14.6	7	3.3	18	13.5	16	8.8	49	9.8	70	14.0
Ab. Neutrophils	<LLN	22	7.0	2	1.0	10	7.5	5	2.7	15	3.0	36	7.2
Abs. Eosinophils	>ULN	11	3.5	8	3.8	4	3.0	3	1.6	16	3.2	43	8.6
Platelet count	<LLN	1	0.3	2	1.0	0	0.0	1	0.5	0	0.0	3	0.6

REF: Appendix Tables 74.1 and 78.1.

Table 24 Marked Laboratory Abnormalities: Hematology Parameters															
		LEF all RA Studies		Placebo Controlled Studies: US301 & MN301								Active Control Study: MN302			
				LEF		PL		MN301/3 SSZ		US301 MTX		MTX		LEF	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Parameter	Criteria			315		210				182		499			
Hb/Hct	>1.24/>0.1 decrease	36	2.7	5	1.6	3	1.4	2	1.5	3	1.7	6	1.2	5	1.0
MCV	>115 fl	0	0.0	0	0.0	1	0.5	0	0.0	1	0.6	4	0.8	0	0.0
WBC	<2.0 G/l	2	0.2	1	0.3	0	0.0	2	1.5	0	0.0	0	0.0	0	0.0
	>18.0 G/l	14	1.1	1	0.3	5	2.4	0	0.0	3	1.7	8	1.6	5	1.0
Neutrophils	<0.5 G/l	1	0.1	1	0.3	0	0.0	3	2.3	0	0.0	0	0	0	0.0
Platelet count	>800 G/l	7	0.5	1	0.3	2	1.0	0	0.0	0	0.0	0	0.0	4	0.8
	<100 G/l	4	0.8	2	0.6	0	0.0	1	0.8	0	0.0	1	0.2	2	0.4

REF: Appendix Tables 75.1, 77.1 and 78.2.

Two LEF patients showed a fall in WBC below 2000. One had a WBC of 1900 which was 2130 six days earlier and 4570 twelve days later. The other patient (US301-16-010) is described below. None of four LEF patients with a platelet count of less than 100,000 showed, upon retesting, a confirmation of the abnormality, making these likely due to platelet clumping. One MTX patient with a platelet count of 98,000, and one SSZ patient with a count of 76,000 were noted.

SERIOUS ADVERSE HEMATOLOGIC EVENTS: A patient receiving LEF as alternate therapy in US301 was found to have neutropenia with a minimum PMN count of 400. This patient is described below; she also showed a five fold increase in LFTs on treatment with PLC.

Subject US301-16-010, a 44 year old female, received 52 weeks of treatment with leflunomide. Over a five month period she developed severe neutropenia. Study medication was discontinued and cholestyramine was administered. Initially the neutropenia was thought to be secondary to myelofibrosis; however, multiple bone marrow biopsies were unsuccessful due to her obesity. Leflunomide plasma levels were 39.0 at study discontinuation, 13.0 six days later, 1.38 at day 90 and undetectable at day 132.

She was treated with folinic acid and G-CSF without any response in the white blood cells. More than 120 days after leflunomide discontinuation when no improvement in her white blood cell count had occurred, she was asked to discontinue ibuprofen; she had been taking this medication for approximately 2 years. Sixty days after discontinuing ibuprofen, the white lood cell count returned to normal; G-CSF was also briefly administered during this period. At day 260, ibuprofen was re-introduced and after 60 days the white blood cell count remained normal. The diagnosis of myelofibrosis was precluded later by a successful biopsy. The patient recovered completely and is doing well. The Investigator assessed the event as related to leflunomide.

AGRANULOCYTOSIS: No patients on LEF demonstrated this; two on SSZ were seen, where it is a known toxicity. These cases are described below.

Subject MN301-32-1002, a 55 year old male, was hospitalized after 6 weeks of treatment with sulfasalazine for severe leukopenia and agranulocytosis. Sulfasalazine was stopped 5 days before admission because the subject felt unwell with fatigue, lethargy, and anorexia. He was diagnosed with a Streptococcus ovalis infection and was treated with antibiotics and G-CSF. Bone marrow aspirate revealed myeloid cells and a severe drug-related neutropenic reaction. White blood cell counts returned to normal 5 days after treatment.

Subject MN-301-8-1113, a 69 year old female, developed sudden agranulocytosis 6 weeks after starting sulfasalazine treatment. Sulfasalazine was discontinued and after 4 weeks, the white blood cell count was normal. The subject was treated with antibiotics only.

NEOPLASIA

The overall malignancy rate in LEF is comparable with that seen in MTX and SSZ and in PLC, as shown in the table below. Calculation of cases per patient-years of exposure also yields values in the same order of magnitute across all groups.

Table 10 Malignancies Reported for All Clinical Trials for All Treatment Groups					
	LEF	PL	MTX	SSZ	Total
Total number of cases	20	3	16	2	41
Total number of patients*	1,576	261	939	204	2864
Patient years†	2,077	226	936	258	
% of patients with malignancy	1.27	1.15	1.94	0.98	1.43

*Includes patients in extension phases of protocols
†Approximate patient years calculated through 10/97.

A listing of all cases of malignancies by treatment group is given in the appendix.

Lymphoproliferative disorders: There were six cases of lymphoprolifersative disorders in this NDA. Three were in LEF patients, two in MTX patient, and one in SSZ patients. The incidence (and incidence per patient-years, data not shown) are of the same order of magnitude in all three groups (se table below).

Table 12 Summary of Lymphoproliferative Disorders				
	LEF	MTX	SSZ	ALL
# of cases	3	1	1	5
Patient years	2077	936	258	
Total number of patients	1576	823	204	2864
Percent	0.22	0.14	0.75	0.21

An additional SSZ case has since been reported. This makes the rates / 1000 patient-years exposure as follows: 2.2 for LEF, 1.4 for MTX, 15.0 for SSZ, and 0.0 for PLC. Obviously the confidence intervals for these figures would be large, especially for SSZ and PLC, where the number of patient-years was very small.

The three cases of lympohproliferative disoreders associated with LEF are described below. One case (US301-53-003 was further studied by an independent pathologist.

Subject MN302-119-1104 was a 67 year old woman who reported an enlarged nodule in the right axilla and was hospitalized for removal of the nodule 36 weeks after administration of leflunomide. Histology revealed partial follicular centrocytic centroblastic Non-Hodgkin's lymphoma of low malignancy. A single lymph node was detected in the iliac lymph nodes 4 months earlier but malignant disease was not suspected. Splenomegaly and mediastinal and mesenteric lymph node enlargement were detected by CT scan. The Investigator assessed the event as related to leflunomide administration.

Subject US301-53-003 was a 60 year old female who presented with a swollen area on the right side of the neck 76 weeks after administration of leflunomide. Two biopsies were performed. The first revealed normal lymph node tissue and the second showed highly atypical cells exhibiting large and hyperchromic nuclei and very prominent nucleoli compatible with Hodgkin's disease mixed cellularity type I. The subject discontinued study medication and was treated with chemotherapy. The subject is in remission. The Investigator assessed the event as related to study medication. The differential diagnosis in this case is Hodgkin's disease versus large cell lymphoma. The diagnosis of large cell lymphoma is based on the following findings. The lymph node shows only partial replacement by neoplasm, a finding more frequently seen in large cell lymphoma than mixed cellularity Hodgkin's disease (MCHD). The immunoblastic morphology of the neoplastic cells is more typical of large cell lymphoma than MCHD.

This neoplasm represents a large cell lymphoma with CD30 expression and unknown EBV status. The available data does not allow determination of whether the development of this neoplasm is secondary to immunomodulatory therapy. However, the overall findings are highly suggestive of a lymphoma developing in the setting of an altered immune state.

The morphology and immunophenotype of this case are unusual but fit well into the group of neoplasms recently reported in the setting of immunomodulatory therapy for rheumatoid arthritis, "Hodgkin's disease and lymphoproliferations resembling Hodgkin's disease in patients receiving long-term low-dose methotrexate therapy," published in the *American Journal of Surgical Pathology 20: 1279-1287, 1996.* It is important to note that based on recently published data, approximately one-third of lymphoproliferative disorders that occur during immunomodulatory therapy for rheumatoid arthritis will spontaneously regress (usually over a period of four to eight weeks) once immunomodulatory therapy is discontinued, without the need for chemotherapy or radiation therapy.[16]

Subject YU205-05-049 was a 74 year old female who had a decrease in hemoglobin and red blood cell count 108 weeks after administration of leflunomide. A bone marrow aspirate was performed and the histopathological examination was consistent with chronic lymphocytic leukemia. The subject received no treatment for the leukemia and completed treatment with leflunomide per protocol. The Investigator assessed the event as not related to leflunomide administration.

INTERSTITIAL PNEUMONITIS

Two cases on LEF were reported, but on review proved to not be interstitial pneumonitis, and five MTX cases with this lesion are described below.

Subject MN302-111-1106, a 67 year old female, entered the study on July 20, 1995. She had a history of corneal ulcer, pneumonia, bronchitis, pleurisy, peripheral nerve decompression and cholecystectomy and was concomitantly suffering from a cataract. On October 5, 1995, after 10 weeks on methotrexate, the patient complained of dry cough, nocturnal dyspnea and shortness of breath on exertion. However, there was no expectoration, no chest pain and no fever. Bilateral inspiratory crackles and bilateral shadowing were present on chest x-ray. Pulmonary tests revealed a restrictive defect with a severe reduction in DL_{CO}. A CT scan of the chest showed a ground glass appearance compatible with methotrexate-associated pneumonitis. The patient was treated with I.V. broad spectrum antibiotics with dramatic improvement in her symptoms. An infection seemed more likely than a diagnosis of pneumonitis. The Investigator assessed the event as possibly related to study medication and methotrexate was discontinued on October 11, 1995.

Subject US301-20-015, a 73 year old female, entered the study on January 2, 1996. She had a history of hypothyroidism, urinary tract infection, and hypercholesterolemia. Four weeks after methotrexate intake, she suffered persistent shortness of breath. Study medication was discontinued one week later on February 13, 1996. Chest x-ray showed diffuse bilateral interstitial infiltrates with multiple nodules. Symptoms persisted and the patient was admitted to the hospital on February 23, 1996. At admission, blood gases revealed a low oxygen content. On February 25, 1996, the chest x-ray showed "slight clearing of the interstitial process". She was treated with high doses of prednisone. The Investigator assessed the event as related to study medication.

Subject MN302-89-1020, a 62 year old male, entered the study on June 6, 1995. After 20 weeks on methotrexate, patient developed interstitial pneumonia with dyspnea, cough, fever and basal crepitations. Chest x-ray showed interstitial changes. Bronchoalveolar lavage showed lymphocytosis and a large number of eosinophils. Bacteriological examinations, including tuberculosis, were negative. The patient was treated with prednisone and received isoniazid and pyridoxine prophylactically for 6 months. A control x-ray after 2 weeks was normal. The Investigator assessed the event as related to study medication.

Subject MN304-115-103, a 51 year old male, entered the study on July 23, 1996. Patient suffered from a pre-existing 8 week long slight shortness of breath which suddenly turned into a severe increase in shortness of breath after methotrexate intake. He was admitted to the emergency room. X-ray and bronchoscopic findings were inconclusive. He was diagnosed with methotrexate pneumonitis. The Investigator assessed the event as possibly related to study medication.

Subject MN304-55-1021, a 72 year old male, was hospitalized for shortness of breath, fever and night sweats after 32 weeks on methotrexate. Chest x-ray showed bilateral nodular shadowing and patchy consolidation in both lungs. CT scan showed fibrosing alveolitis. He was treated with prednisone and antibiotics. His condition deteriorated which led to death. Investigator assessment is not available.

Subject MN302-30-1018, a 55 year old female, entered the study on October 31, 1995. On April 25, 1996 she presented with fever and shortness of breath. Leflunomide was discontinued. The subject was evaluated the following day with fever, left flank pain, weight loss, tachypnea and tachycardia. She was admitted to the hospital with a diagnosis of hyperthyroidism and possible pulmonary embolus. A pulmonary specialist confirmed the absence of pulmonary abnormalities. Thyroid function tests indicated hyperthyroidism. The subject recovered with treatment. Clarification of the event and the appropriate diagnosis occurred after the database was locked.

Subject MN302-41-1007, a 59 year old male, was reported to have dyspnea secondary to lung fibrosis 12 weeks after starting on leflunomide. Lung fibrosis was a concomitant disease and was present at study entry. The Investigator assessed the event as not related to leflunomide.

REVERSIBLE RENAL FAILURE

No case of renal failure was seen in the LEF group. Three cases were seen on MTX, consistent with the known risk, especially in the presence of prerenal states and/or other concomitant nephrotoxic agents.

Subject MN302-54-1002, a 59 year old female, with a history of hypertension and diabetes mellitus, was hospitalized 19 weeks after starting methotrexate for shortness of breath and retrosternal pain; she was tachypneic at rest, had a regular pulse and her blood pressure was 150/90 mm Hg. She had developed a pansystolic murmur, heard best at the cardiac apex and bilateral basal fine inspiratory crackles. Cardiac enzymes were normal. ECGs showed ST depression in leads V2 and V6 and in lead I. Bilateral basal congestion was noted by chest x-ray. She suffered from further episodes of chest pain which were self-limiting and not associated with further changes in the ECG. Her condition was complicated by an exacerbation of diabetes mellitus and a urinary tract infection with E. coli which was treated with Trimethoprim. She developed acute renal failure. Trimethoprim and NSAIDs were discontinued and cautious fluid treatment was given. Her renal and cardiac failure subsided slowly. The Investigator assessed the event as not related to methotrexate but to the underlying disease.

Subject MN302-79-1001, a 67 year old female with a history of varicose veins, was hospitalized 28 weeks after starting methotrexate for leukopenia, anemia, thrombocytopenia, abnormal renal function, dyspnea, fever and chest pain. After one week in the hospital, her condition deteriorated further and she developed agranulocytosis and kidney and liver failure. The patient required intensive care and was put on mechanical ventilation. She was treated with G-CSF and recovered after 3 weeks of treatment. The Investigator concluded that at admission, she received high dose I.V. Diclofenac 225 mg/day which might have caused acute renal failure and led to methotrexate intoxication. The agranulocytosis and liver impairment were attributed to the relative methotrexate overdose.

Subject US301-12-011, a 65 year old female, was hospitalized 29 weeks after starting on methotrexate for the acute onset of renal failure. She was seen in the emergency room the week prior to admission with a history of vomiting and diarrhea. The subject was treated for dehydration and no laboratory tests were performed. At week 29, she was seen by the Principal Investigator for mouth ulcers and epistaxis. Laboratory tests were compatible with acute renal failure. She was treated with I.V. fluids and packed red cells and subsequently recovered. In the opinion of the nephrologist and the Investigator, renal failure developed as a result of severe dehydration, nausea and vomiting over a two week period in a patient receiving methotrexate.

RENAL AND URICOSURIC EFFECTS:

Leflunomide is known to effect the brush border of the renal proximal tubule resulting in uricosuria. A trend to hypophosphatemia was seen in the data, but these two effects did not coexist. No systematic effect was seen on creatinine and calcium. These results are displayed in the next three tables.

Table 28 Summary Statistics for Laboratory Values - Renal Function						
Variables	Placebo-Controlled Studies: US301 & MN301				Active Control Study: MN302	
	LEF Combined	PL Combined	MN301/3 SSZ	US301 MTX	MTX	LEF
Creatinine (µmol/l)						
N	314	209	133	180	493	495
Baseline Mean	87.02	88.02	91.18	89.49	88.90	89.07
Endpoint Mean	87.38	88.30	91.43	91.39	92.24	89.27
Mean Change	0.36	0.28	0.25	1.90	3.34	0.20
Urea Nitrogen (mmol/l)						
N	303	206	124	180	467	476
Baseline Mean	5.63	5.61	6.09	5.61	5.65	5.65
Endpoint Mean	5.28	5.61	5.69	5.34	5.51	5.24
Mean Change	-0.35	0.00	-0.40	-0.27	-0.14	-0.41
Uric Acid (µmol/l)						
N	304	206	124	180	467	476
Baseline Mean	294.60	291.79	308.42	298.11	290.88	285.84
Endpoint Mean	233.19	293.16	292.82	299.86	302.81	223.65
Mean Change	-61.41	1.37	-15.60	1.75	11.93	-62.19
Calcium (mmol/l)						
N	314	209	133	180	493	495
Baseline Mean	2.25	2.24	2.23	2.27	2.22	2.21
Endpoint Mean	2.24	2.25	2.25	2.28	2.23	2.22
Mean Change	-0.01	0.01	0.02	0.01	0.01	0.01
Phosphorus (mmol/l)						
N	301	206	122	180	462	471
Baseline Mean	1.14	1.13	1.15	1.14	1.14	1.14
Endpoint Mean	1.01	1.13	1.12	1.15	1.10	1.01
Mean Change	-0.13	0.01	-0.03	0.01	-0.04	-0.13

REF: Appendix Table 71.1.

Table 29 Shifts from Normal at Baseline to Abnormal at Endpoint or at Two Evaluations: Renal Function Tests														
		Placebo-Controlled Studies: US301 & MN301								Active Control Study: MN302				
		LEF		PL		MN301/3 SSZ		US301 MTX		MTX		LEF		
		N	%	N	%	N	%	N	%	N	%	N	%	
Parameter	Criteria	315		210		133		182		498		501		
Creatinine	>ULN	4	1.3	2	1.0	1	0.8	4	2.2	12	2.4	4	0.8	
Uric Acid	<LLN	47	15.0	3	1.4	5	3.8	3	1.6	3	0.6	56	11.2	
Phosphorus	<LLN	25	8.0	3	1.4	1	0.8	3	1.6	6	1.2	19	3.8	
Calcium	<LLN	52	16.5	22	10.5	16	12.0	23	12.6	83	16.7	99	19.8	

REF: Appendix Table 74.1.

Table 30 Marked Laboratory Abnormalities: Renal Function Tests															
		LEF all RA Studies		Placebo-Controlled Studies: US301 & MN301								Active Control Study: MN302			
				LEF		PL		MN301/3 SSZ		US301 MTX		MTX		LEF	
		N	%.	N	%	N	%	N	%	N	%	N	%	N	%
Parameter	Criteria	1339		315		210		133		182		498		501	
Creatinine/BUN	≥159 umol/l ≥14.3 mmol/l	3	0.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Uric Acid	<75 umol/l	21	1.6	1	0.3	0	0.0	0	0.0	2	1.1	0	0.0	2	0.4
	>550 umol/l	11	0.9	2	0.7	5	2.4	3	2.4	8	4.4	6	1.3	0	0.0
Phosphorus	<0.55 mmol/l	15	1.2	3	1.0	0	0.0	1	0.8	0	0.0	0	0.0	7	1.4
Calcium	<1.7 mmol/l	14	1.1	0	0.0	1	0.5	0	0.0	0	0.0	2	0.4	0	0.0

REF: Appendix Tables 75.1 and 77.1.

OTHER POSSIBLY CLINICALLY SIGNIFICANT ADVERSE EVENTS

WEIGHT LOSS: There was concern from the early Yugoslovia study (YU204) that weight loss was overrepresented in LEF patients. In the combined controlled NDA database, weight loss was reported in 2.0% of LEF patients, compared to 1.3% in MTX, 1.5% for SSZ, and 0.4% in PLC. Details of these AEs are given in the appendix.

ALOPECIA: An association of alopecia was found in controlled comparisons: 8.9% for LEF compared to 1.4% in PLC, and, in the active-controlled trial, 16.2% in LEF compared to 9.8% in MTX. In the controlled trials eight LEF, three MTX, and one PLC patient withdrew for alopecia. Of the eight LEF patients, alopecia resolved in all eight. Two of the three MTX patients resolved. The patient on PLC has continued to show alopecia. Data for these AEs are in the appendix.

DIGESTIVE SYMPTOMS: Diarrhea, abdominal pain, nausea/vomiting, and oral ulcerations occurred greater in LEF than in PLC. The rates for these events are given below, separately for the placebo-controlled and the active-controlled data:

	LEF v MTX v SSZ v PLC (%)				LEF v MTX (%)	
diarrhea	26.7	19.2	9.8	11.9	22.2	10.0
abd. pain.	10.8	15.4	10.5	8.1	13.8	11.2
nausea/vomiting	17.8	19.2	22.6	14.3	14.6	20.1
oral ulcers	4.8	9.9	3.0	3.8	3.4	5.6

ALLERGIC / CUTANEOUS REACTIONS: Allergic reactions occurred at a rate of 4.8%, compared to 2.4% in placebo, in the controlled studies. Rash occurred in 12.4% compared to 6.7%, and pruritis 4.8% compared to 1.9% in the same database. A more complete listing of allergic AEs is given in the appendix.

INFECTIONS: Infections were common in all cohorts in these RA trials. The table below lists the rates for various COSTART codes.

	LEF v MTX v SSZ v PLC (%)				LEF v MTX (%)	
upper resp. inf.	21.0	31.9	20.3	20.5	26.5	24.5
bronchitis	5.1	6.6	3.8	1.9	8.0	6.8
flu syndrome	3.5	7.1	0.0	2.4	0.0	0.0
pneumonia	3.2	1.1	0.0	0.0	2.2	2.2

The analysis below of certain, specific infections was unrevealing.

Table 2 Summary of Patients with Specified Infection

	LEF all RA Studies		Placebo-Controlled Studies: US301 & MN301								Active Control Study: MN302			
			LEF		PL		MN301/3 SSZ		US301 MTX		MTX		LEF	
Criteria	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total Patients	1339		315		210		133		182		498		501	
H. Simplex	18	1.3	4	1.3	1	0.5	3	2.3	10	5.5	12	2.4	11	2.2
H. Zoster	16	1.2	1	0.3	0	0.0	2	1.5	2	1.1	9	1.8	8	1.6
Sepsis	1	0.1	1	0.3	1	0.5	2	1.5	1	0.5	0	0.0	0	0.0
Opportunistic Infection	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

The appendix details features -- duration, severity, relatedness, treatment, outcome, and cumulative incidence -- of all patients with infections in the pivotal trials.

H. SPECIAL PATIENT GROUPS

The following tables explore subset responses by demographic markers and other clinically subsets to determine if any major differences in outcomes were seen. In general these analyses were non-revealing, except for known descriptors of, or risk factors for, severe RA, such as disease duration, and failure of prior DMARD, or surrogates for these features, such as corticosteroid use. The question of whether the use of concomitant diclofenac altered outcome was also examined.

Table 33 ACR Success by Gender

Study and Treatment Group	ACR Success					
	Leflunomide		Placebo		Active	
	n/N	%	N/N	%	n/N	%
Pivotal Studies						
US301 (12 months)						
Men	23/50	46.0	6/35	17.1	17/45	37.8
Women	51/132	38.6	16/83	19.3	46/135	34.1
MN301 (6 months)						
Men	15/35	42.9	7/23	30.4	18/40	45.0
Women	48/99	48.5	19/68	27.9	41/92	44.6
Active-Controlled Studies						
MN301/303 (12 mos.)						
Men	11/31	35.5	NA		16/40	40.0
Women	48/99	48.5	NA		36/92	39.1
MN302						
Men	53/145	36.6	NA		73/140	52.1
Women	162/350	46.3	NA		204/349	58.5

REF: Appendix Table 129

Table 34 ACR Success by Age

Study and Treatment Group	ACR Success					
	Leflunomide		Placebo		Active	
	n/N	%	n/N	%	n/N	%
Pivotal Studies						
US301 (12 months)						
<65	56/141	39.7	17/97	17.5	54/145	37.2
>=65	18/41	43.9	5/21	23.8	9/35	25.7
MN301 (6 months)						
<65	41/88	46.6	15/65	23.1	35/81	43.2
>=65	22/42	52.4	11/26	42.3	24/51	47.1
Active-Controlled Studies						
MN301/303 (12 mos.)						
<65	41/88	46.6	NA		32/81	39.5
>=65	18/42	42.9	NA		20/51	39.2
MN302						
<65	158/344	45.9	NA		196/343	57.1
>=65	57/151	37.7	NA		81/146	55.5

REF: Appendix Table 98

Table 35 ACR Success by Duration of RA						
	ACR Success					
Study and Treatment Group	Leflunomide n/N	%	Placebo n/N	%	Active n/N	%
Pivotal Studies						
US301 (12 months)						
≤2 yrs	31/71	43.7	3/39	7.7	29/73	39.7
>2 yrs	43/111	38.7	19/78	24.4	34/107	31.8
MN301 (6 months)						
≤2 yrs	25/48	52.1	12/41	29.3	24/55	43.6
>2 yrs	38/82	46.3	14/50	28.0	35/77	45.5
Active-Controlled Studies						
MN301/303 (12 mos.)						
≤2 yrs	22/48	45.8	NA		26/55	47.3
>2 yrs	37/82	45.1	NA		26/77	33.8
MN302 (12 mos.)						
≤2 yrs	103/218	47.2	NA		124/214	57.9
>2 yrs	112/277	40.4	NA		153/275	55.6

REF: Appendix Table 161

Table 36 ACR Success by Prior DMARD Use						
	ACR Success					
Study and Treatment Group	Leflunomide n/N	%	Placebo n/N	%	Active n/N	%
Pivotal Studies						
US301 (12 months)						
No prior DMARD use	33/81	40.7	5/47	10.6	25/79	31.6
Prior DMARD use	41/101	40.6	17/71	23.9	38/101	37.6
MN301 (6 months)						
No prior DMARD use	27/51	52.9	14/48	29.2	30/67	44.8
Prior DMARD use	36/79	45.6	12/43	27.9	29/65	44.6
Active-Controlled Studies						
MN301/303 (12 mos.)						
No prior DMARD use	24/51	47.1	NA		30/67	44.8
Prior DMARD use	35/79	44.3	NA		22/65	33.8
MN302						
No prior DMARD use	79/168	47.0	NA		97/163	59.5
Prior DMARD use	136/327	41.6	NA		180/326	55.2

REF: Appendix Table 193

Table 37 ACR Success by Concomitant Use of Corticosteroids						
	ACR Success					
Study and Treatment Group	Leflunomide n/N	%	Placebo n/N	%	Active n/N	%
Pivotal Studies						
US301 (12 months)						
No corticosteroids	33/84	39.3	13/53	24.5	29/84	34.5
Corticosteroids	41/98	41.8	9/65	13.8	34/96	35.4
MN301 (6 months)						
No corticosteroids	38/70	54.3	16/50	32.0	33/71	46.5
Corticosteroids	25/60	41.7	10/41	24.4	26/61	42.6
Active-Controlled Studies						
MN301/303 (12 mos.)						
No corticosteroids	36/70	51.4	NA		36/71	50.7
Corticosteroids	23/60	38.3	NA		16/61	26.2
MN302						
No corticosteroids	62/141	44.0	NA		110/171	64.3
Corticosteroids	153/354	43.2	NA		167/318	52.5

REF: Appendix Table 225

Table 38 ACR Success by Concomitant Use of NSAIDs						
	ACR Success					
Study and Treatment Group	Leflunomide		Placebo		Active	
	n/N	%	n/N	%	n/N	%
Pivotal Studies						
US301 (12 months)						
No NSAIDs	19/45	42.2	9/41	22.0	17/54	31.5
NSAIDs	55/137	40.1	13/77	16.9	46/126	36.5
MN301 (6 months)						
No NSAIDs	5/17	29.4	4/12	33.3	12/28	42.9
NSAIDs	58/113	51.3	22/79	27.8	47/104	45.2
Active-Controlled Studies						
MN301/303 (12 mos.)						
No NSAIDs	6/17	35.3			11/28	39.3
NSAIDs	53/113	46.9			41/104	39.4
MN302						
No NSAIDs	38/97	39.2			34/67	50.7
NSAIDs	177/398	44.5			243/422	57.6

REF: Appendix Table 257

Table 39 ACR Success by Concomitant Use of Diclofenac						
	ACR Success					
Study and Treatment Group	Leflunomide		Placebo		Active	
	n/N	%	n/N	%	n/N	%
Pivotal Studies						
US301 (12 months)						
No Diclofenac	66/166	41.0	21/112	18.8	59/170	34.7
Diclofenac	6/16	37.5	1/6	16.7	4/10	40.0
MN301 (6 months)						
No Diclofenac	39/78	50.0	18/57	31.6	42/94	44.7
Diclofenac	24/52	46.2	8/34	23.5	17/38	44.7
Active-Controlled Studies						
MN301/303 (12 mos.)						
No Diclofenac	37/78	47.4			41/94	43.6
Diclofenac	22/52	42.3			11/38	28.9
MN302						
No Diclofenac	144/331	43.5			187/327	57.2
Diclofenac	71/164	43.3			90/162	55.6

REF: Appendix Table 407

I. CONCLUSION

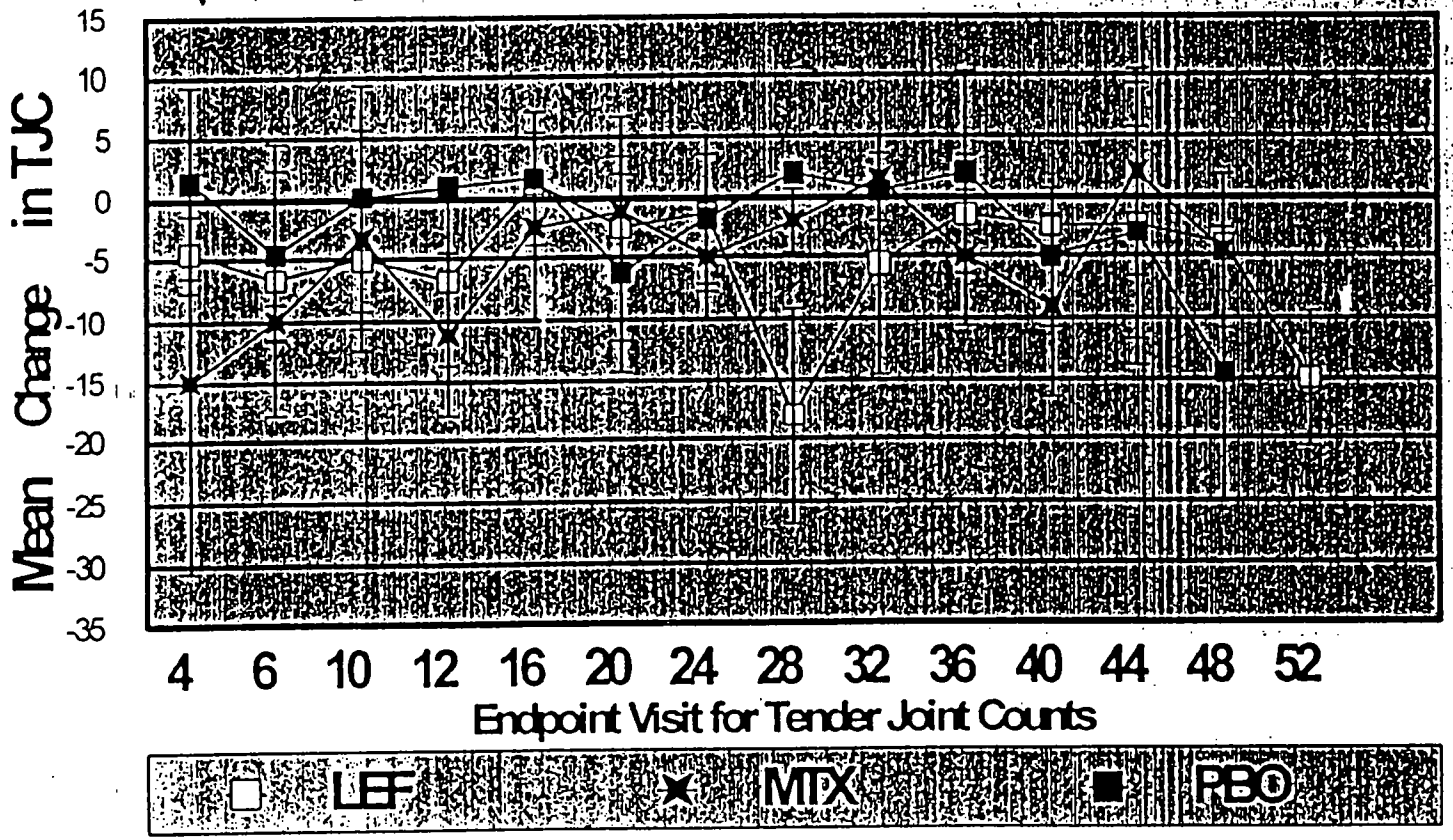
The LEF safety profile is qualitatively adequate to merit approval based on the overall risk/benefit analysis, and quantitatively large enough to enable sufficient description of risks in the label (attached). As with other currently assessed "immunoactive" RA drugs, the sponsor should participate in a phase 4 program to better quantitate rates of rare but serious adverse events (including lymphoproliferative disorders and opportunistic infections) compared to alternative therapies and to conservative therapy.

9/3/98

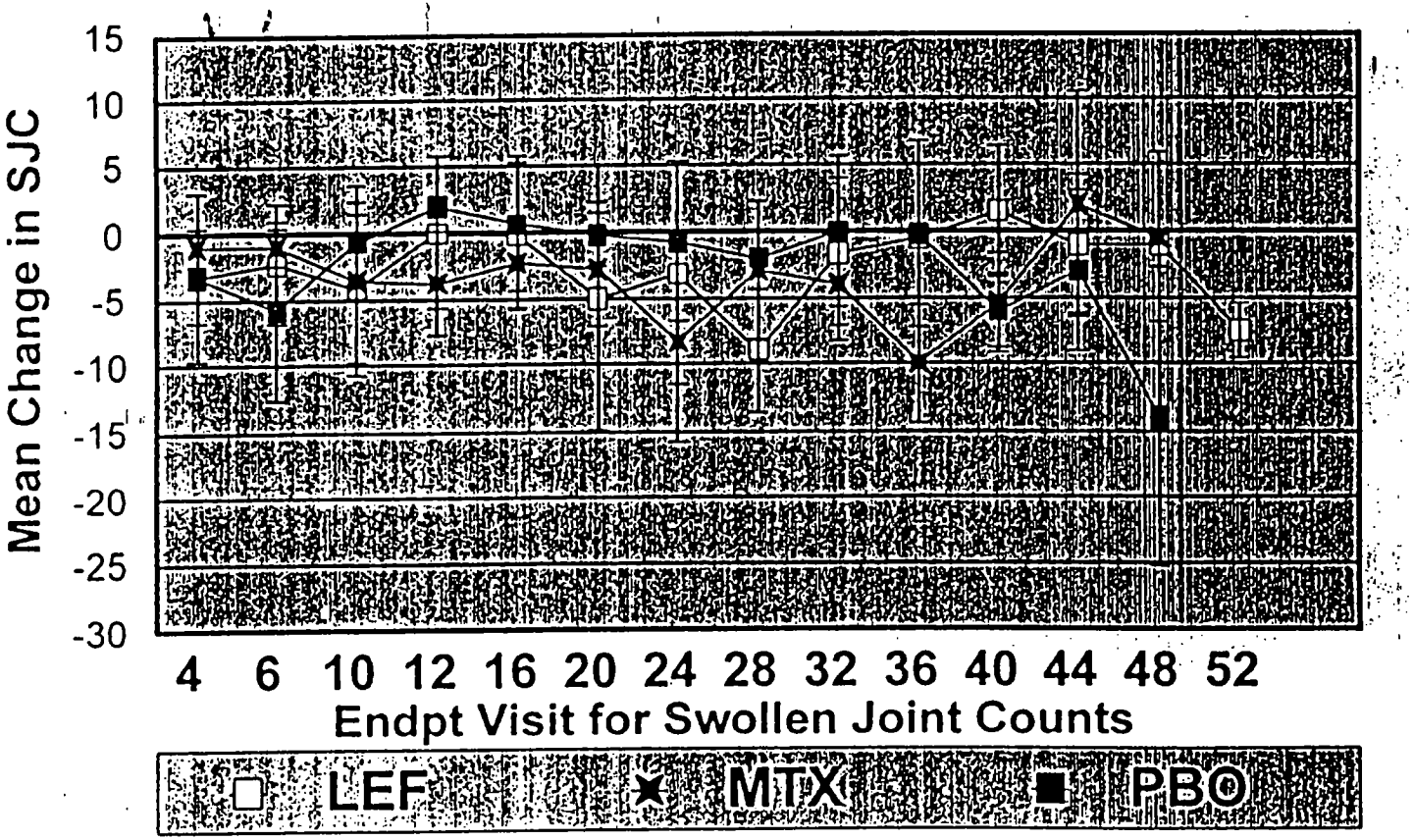
JEH 9-3-98

APPENDICES

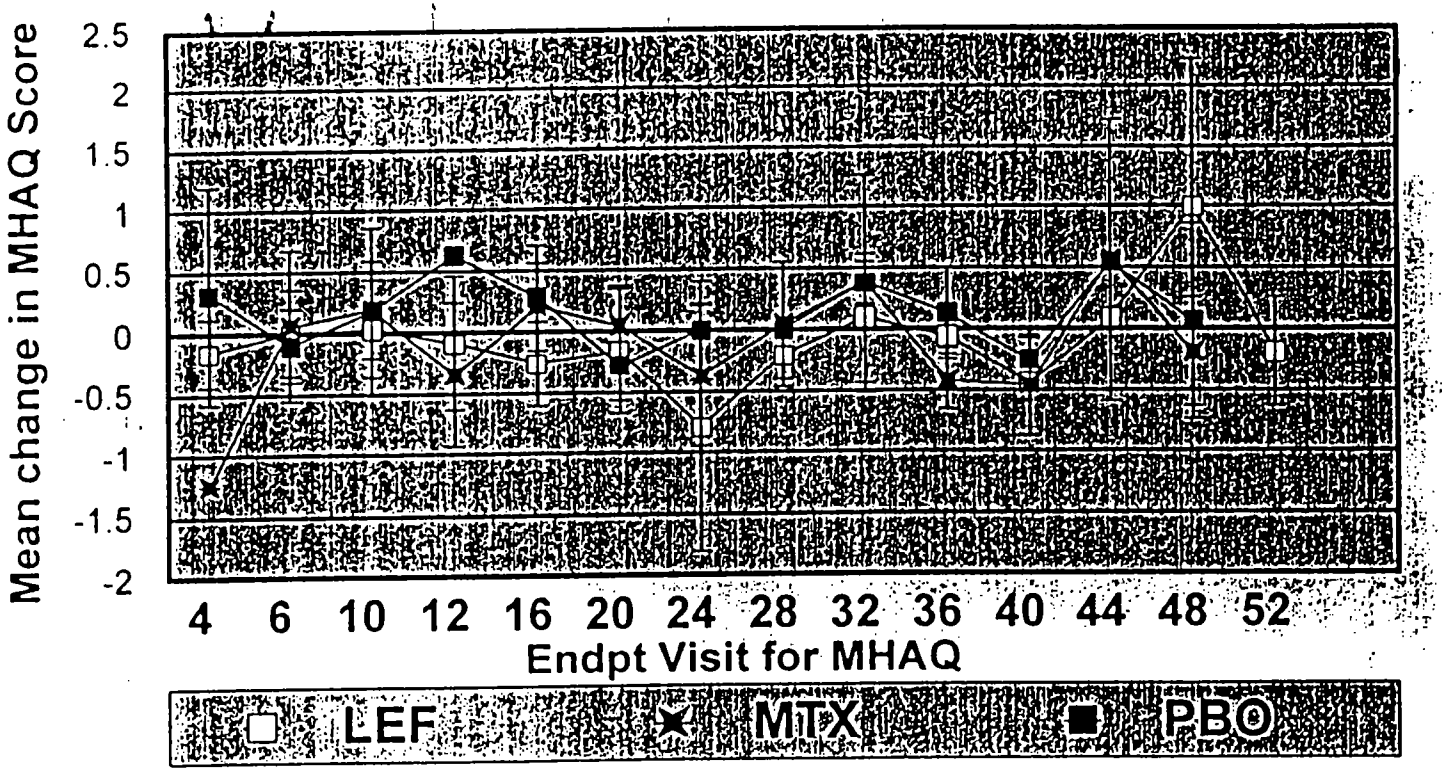
Mean Change in TJC(+/- SD) vs Endpoint Visit for US301 Dropouts



Mean Change in SJC (+/- SD) vs Endpoint Visit for US301 Dropouts



Mean Change in MHAQ Score (+/-SD) vs Endpoint Visit in US301 Dropouts



Subject MN301-33-1002, a 51 year old female, entered the study on July 21, 1994. Prior to treatment, at screening visit (180/90) and baseline (160/120) the patient had labile hypertension not previously documented or treated. The subject was hospitalized on September 7, 1994, due to papilledema, vomiting and drowsiness after 8 weeks on leflunomide. Symptoms started on September 1, 1994, when she developed a pounding frontal headache and blood pressure was noted to be 230/115. She had signs of grade 3-4 retinopathy. The subject was treated initially with calcium channel blockers but blood pressure again increased. The subject was re-admitted to the hospital and treated with beta blockers and the blood pressure was controlled. Chest x-ray was normal and ECG showed left ventricular hypertrophy. Renal diagnostic tests (creatinine clearance, duplex ultrasound and VMA) showed no abnormalities. The Investigator assessed the malignant hypertension as possibly related to leflunomide, but assessed the labile hypertension at study entry and subsequent re-elevation as not related to study drug administration.

Table 11	Listing of all Malignancies by Treatment Group							
Study	Inv.	Pat. ID	TX	Site/Diagnosis of Cancer/Malignancy	Age	Duration Tx	Date	Site
*YU203	05	05-5008	L	Liposarcoma - r. hemithorax Hypernephroma - r. kidney	71	960	1-Aug-93	Thorax and Kidney
YU203	04	04-0036	L	Breast cancer (right)	52	5	9-Jul 91	Breast
YU205	04	04-0002	L	Basal cell carcinoma	61	287	23-Mar-92	Skin
YU205	05	05-0049	L	Chronic lymphocytic leukemia	73	673	7-Sep-93	Blood/ BM
YU207	02	02-0227	L	Endometrial neoplasm/ carcinoma cervix/ovarian cyst	48	70	14-Dec-92	Cervix/uterus
YU207	02	02-0229	L	Adenocarcinoma of lung	56	110	30-Jan-93	Lung
MN302	24	24-1003	L	Rectal carcinoma (death) - liver metastases	71	15	14-Oct-94	Rectum
MN302	56	56-1005	L	Basal cell carcinoma	68	128	15-Nov-95	Skin
MN302	120	120-1105	L	Adenocarcinoma Hepatic ducts	70	246	29-Mar-96	Liver
MN302	119	119-1104	L	Non-Hodgkin's lymphoma	67	169	17-Jun-96	Blood/BM
MN303	26	26-1008	L	Breast cancer (bilateral)	70	187	28-May-96	Breast
MN304	46	46-1002	L	Esophageal cancer (death)	59	685	Mar-96	Esophagus
MN304	37	37-1002	L	Breast cancer (left)	67	757	9-Jul-96	Breast
MN304	73	73-1003	L	Basal cell carcinoma left breast	76	541	7-Aug-96	Skin
MN304	99	99-1018	L	Ovarian cancer	71	365	15-Oct-96	Ovary
US301	11	11-009	L	Transitional cell carcinoma of left kidney	62	239	16-Oct-95	Kidney
US301	54	54-009	L	Carcinoma uterus	59	259	1-Dec-96	Uterus
US301	26	26-014	L	Carcinoma breast	59	543	1-Jul-97	Breast
US301	53	53-003	L	Hodgkin's Disease, mixed cellularity type 1	60	538	14-Jul-97	Blood/BM
MN304	89	89-1006	L	Adenocarcinoma of lung	52	413	14-Apr-96	Lung
MN302	67	67-1001	M	Basal cell carcinoma (left side of face)	68	36	1-Oct-94	Skin
MN302	07	07-1006	M	Basal cell carcinoma	73	176	Jul-94	Skin
MN302	14	14-1007	M	Malignant neoplasm	70	326	1-Feb-96	Skin
MN302	115	115-1127	M	Ovarian carcinoma (death)	68	344	1-Oct-96	Ovarian
MN302	19	19-1021	M	B-cell lymphoma (death)	67	75	11-Sep-95	Blood/BM
MN304	55	55-1011	M	Prostatic cancer	75	378	20-Jul-95	Prostate
MN304	59	59-1008	M	Breast cancer (left)	45	561	18-Jun-96	Breast
MN304	92	92-1003	M	Colon cancer	71	1031	26-Jun-97	Colon
US301	40	40-011	M	Carcinoma lung	56	-6	10-Jul-95	Lung
US301	31	31-005	M	Carcinoma breast	64	73	11-Oct-95	Breast
US301	31	31-003	M	Carcinoma cervix	62	345	25-Jun-95	Cervix
US301	01	01-005	M	Carcinoma bladder	69	258	27-Dec-96	Bladder
US301	21	21-009	M	Basal cell carcinoma	55	601	17-Apr-97	Skin
MN304	131	131-1101	M	Basal cell carcinoma	63		2 May 97	Skin
MN304	53	53-1012	M	Colon cancer	67		1 July 97	Colon
MN304	70	70-1007	M	Basal cell carcinoma	63		-	Skin
US301	27	27-1103	P	Ovarian carcinoma	52	138	25-Oct-95	Ovary
US301	23	23-012	P	Adenocarcinoma of prostate/ carcinoma skin	69	345	10-Sep-96	Skin and prostate
US301	32	32-016	P	Carcinoma prostate	64	377	13-Nov-96	Prostate
MN305	20	20-1108	S	Microcellular carcinoma of lung (death)	68	425	15-Jul-95	Lung
MN305	13	13-1002	S	Non-Hodgkin's lymphoma	74	599	4-Dec-95	Blood/BM
MN302	60	60-A002	-	Non-specific cancer/ liver metastases	72	N/A	NA	Liver

*Patient YU203-5008 was treated with leflunomide for 6 months. More than 2 years after stopping the drug, a liposarcoma and a hypernephroma were diagnosed

Tx = treatment: Leflunomide, Placebo, Methotrexate, Sulfasalazine.

Table 4 Summary of Patients with Weight Decrease as an Adverse Event

	LEF all RA Studies		Placebo-Controlled Studies: US301 & MN301								Active Control Study: MN302			
			LEF		PL		MN301/3 SSZ		US301 MTX		MTX		LEF	
Criteria	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total Patients	1339		315		210		133		182		498		501	
Occurrence	47	3.5	7	2.2	1	0.5	2	1.5	0	0.0	9	1.8	9	1.8
AE	47	3.5	7	2.2	1	0.5	2	1.5	0	0.0	9	1.8	9	1.8
Study Treatment														
Discontinued	5	0.4	3	1.0	0	0.0	1	0.8	0	0.0	1	0.2	0	0.0
Duration														
Mean	123.56		49.57		127.00		74.00		0		139.71		186.4	
2 days or less	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
3 to 28 days	5	0.4	4	1.3	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Greater than 28 days	25	1.9	3	1.0	1	0.5	1	0.8	0	0.0	7	1.4	7	1.4
Severity														
Mild	17	1.3	2	0.6	0	0.0	1	0.8	0	0.0	3	0.6	5	1.0
Moderate	27	2.0	4	1.3	1	0.5	1	0.8	0	0.0	6	1.2	4	0.8
Severe	3	0.2	1	0.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Relatedness														
Not Related	10	0.7	2	0.6	0	0.0	0	0.0	0	0.0	1	0.2	1	0.2
Possibly Related	37	2.8	5	1.6	1	0.5	2	1.5	0	0.0	8	1.6	8	1.6
Treatment														
None	2	0.1	2	0.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Drugs/Therapy	45	3.4	5	1.6	1	0.5	2	1.5	0	0.0	9	1.8	9	1.8
Outcome														
Resolved	30	2.2	6	1.9	0	0.0	0	0.0	0	0.0	7	1.4	7	1.4
Continuing	17	1.3	1	0.3	1	0.5	2	1.5	0	0.0	2	0.4	2	0.4
≥10% Loss	161	13.1	18	5.8	11	5.3	2	1.5	8	4.4	16	3.3	48	9.6

REF: Appendix Tables 54.1, 54.3, and 384; MN302 Study Report Table 123

Table 19 Summary of Patients with Alopecia as an Adverse Event

Criteria	LEF all RA Studies		Placebo-Controlled Studies: US301 & MN301								Active Control Study: MN302			
			LEF		PL		MN301/3 SSZ		US301 MTX		MTX		LEF	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total Patients	1339		315		210		133		182		498		501	
Occurrence	130	9.7	28	8.9	3	1.4	8	6.0	11	6.0	49	9.8	81	16.2
AE	130	9.7	28	8.9	3	1.4	8	6.0	11	6.0	49	9.8	81	16.2
SAE	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Study Treatment														
Discontinued	8	0.6	1	0.3	1	0.5	0	0.0	2	1.1	1	0.2	7	1.4
Duration														
Mean	116.1		90.66		115.5		93.13		69.2		150.8		134.2	
2 days or less	2	0.1	2	0.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
3 to 7 days	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
8 to 28 days	4	0.3	1	0.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Greater than 28 days	79	5.9	13	4.1	2	1.0	8	6.0	5	2.7	19	3.8	55	11.0
Severity														
Mild	79	5.9	20	6.3	1	0.5	5	3.8	8	4.4	32	6.4	50	10.0
Moderate	48	3.6	7	2.2	2	1.0	3	2.3	3	1.6	14	2.8	31	6.2
Severe	3	0.2	1	0.3	0	0.0	0	0.0	0	0.0	3	0.6	0	0.0
Relatedness														
Not Related	1	0.1	0	0.0	0	0.0	1	0.8	1	0.5	0	0.0	0	0.0
Possibly Related	124	9.3	23	7.3	2	1.0	7	5.3	8	4.4	49	9.8	81	16.2
Probably Related	5	0.4	5	1.6	1	0.5	0	0.0	2	1.1	0	0.0	0	0.0
Treatment														
None	17	1.3	17	5.4	1	0.5	0	0.0	11	6.0	0	0.0	0	0.0

Table 19 Summary of Patients with Alopecia as an Adverse Event

Criteria	LEF all RA Studies		Placebo-Controlled Studies: US301 & MN301								Active Control Study: MN302			
			LEF		PL		MN301/3 SSZ		US301 MTX		MTX		LEF	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Drugs/Therapy	113	8.4	11	3.5	2	1.0	8	6.0	0	0.0	49	9.8	81	16.2
Outcome														
Resolved	81	6.0	15	4.8	2	1.0	6	4.5	4	2.2	16	3.2	53	10.6
Resolved w/Sequelae	3	0.2	0	0.0	0	0.0	0	0.0	1	0.5	1	0.2	3	0.6
Continuing	46	3.4	13	4.1	1	0.5	2	1.5	6	3.3	32	6.4	25	5.0
Cumulative Incidence (KMA%)														
1 month or less		--		1.0		0.0		1.6		0.6		1.2		1.6
3 months or less		--		4.2		1.1		2.5		1.7		3.0		8.0
6 months or less		--		11.1		1.9		5.8		4.5		5.9		16.1
9 months or less		--		12.7		1.9		7.1		6.2		8.8		17.9
12 months or less		--		12.7		1.9		9.1		8.0		10.1		18.6

REF: Appendix Tables 54.1, 54.3, 64.1, 64.2 and 374; US301 Study Report p. 158; MN302 Study Report Tables 110, 111 and 123.

Table 1 — Review of HTN Adverse Event Cases in Leflunomide Subjects in Phase III Clinical Trials

Pt. Number	HTN Baseline: Hx at BL	HTN Baseline: Elev. BP	Relevant Hx	BP Baseline	Range during Study: Systolic	Range during Study: Diastolic	Endpoint	Concomitant Meds: NSAID	[illegible]	HTN	Concomitant Illness	Comments and Conclusion	Controlled
A. 301MN													
14-1109	0	1	0	175/85	130-165	80-110	130/80	[illegible]	0	nif to Enalapril		Switched from Nifedipine to Enalapril	1
15-1102	0	1	0	135/85	140-170	70/85	130/80	diclofenac	1	Diltiazem		Maintained same dose	1
17-1105	1	1	0	160/100	130-160	80-110	160/100	0	1	HCTZ/Triamterene		Poorly controlled BP, HCTZ for edema	0
20-1120	1	1	0	170/80	140-180	80-105	160/85	ketoprofen	0	amlodipine		No adjustment to meds	0
28-1008	0	1	0	160/90	165-220	90-105	190/80	naproxen	1	[illegible] to enalapril		Pred for asthma, switched to enalapril & inc	0
33-1002	0	1	croup HTN	160/90	140-220	80-130	230/130	diclofenac	0	nif, [illegible], [illegible]		SAE, see CIOMS report	0
33-1004	0	0	0	140/90	115-135	80-100	115/80	diclofenac	0	[illegible]			1
6-1107	1	1	0	150/90	135-160	80-100	160/100	[illegible] to diclof	1	HCTZ, enalapril		Switched from naproxen to diclofenac	0
B. 302MN													
10-1001	0	1	0	150/90	130-205	80-120	200/110	[illegible], [illegible]	0	[illegible], [illegible]			0
107-1102	0	0	0	145/80	135-170	85-115	150/85	[illegible]	1	0		No anti-HTN meds given	1
115-1105	0	0	albuminuria/hematuria	150/80	130-160	85-100	130/80	[illegible], dicl.	0	nif, amlodipine			1
115-1124	0	1	0	170-80	140-200	80-130	160/80	dicl	0	lisinopril, amlodipine			0
115-1125	1	0	0	130/80	120-150	80-100	130/100	0	0	[illegible]			1
117-1105	0	0	0	140/95	120-150	80-100	130/85	[illegible]	0	0			1
117-1107	1	1	0	160/100	130-170	80-120	130/80	ketoprofen	0	[illegible], nif			1
119-1104	1	1	albuminuria	185/105	135-230	80-120	210/105	dicl	0	[illegible], nif, [illegible]		Most of the time BP controlled	1
15-1009	1	0	0	140/90	110-160	70-100	140/80	dicl	1	[illegible] to [illegible] to nif		Most of the time BP controlled	1
17-1007	1	0	0	140/80	120-195	70-110	170/100	dicl	0	hctz, [illegible], [illegible]			1
17-1013	1	0	0	140/85	140-170	85-110	160/80	dicl	1	[illegible], capto, [illegible]			1
18-1003	0	0	0	140/80	120-200	80-100	170/80	dicl	0	0		Only one visit with 200/95	1
19-1001	0	0	0	140/90	125-150	80-105	140/80	naproxen	1	nif			1
20-1006	0	1	0	165/85	175-190	80-100	150/100	[illegible]	0	0			0
30-1012	0	0	0	130/85	120-180	80-85	165-100	dicl	0	0			1
30-1020	0	0	0	140/85	110/200	70-100	160/80	dicl	1	captopril		Only one visit with 200/100	1
31-1008	0	0	0	145/80	140-175	80-100	140/80	naproxen	1	[illegible]		BP allowed to run high	0
31-1015	0	1	0	150/90	140-180	80-105	180/95	dicl	0	[illegible], [illegible], [illegible] to nif		BP gradually increased	0
31-1016	0	0	0	140/80	135-160	70-95	145/80	dicl	1	0			1
34-1009	1	1	0	160/86	120-154	70-108	130/70	ASA	0	[illegible] to [illegible]			1
36-1005	1	0	0	140/95	120-170	80-110	160/110	[illegible] dicl	1	captopril, nif		didn't address BP treated aggressively	0
38-1002	0	0	0	135/80	110-145	70-95	140/95	0	0	captopril			1
43-1013	1	0	0	130/80	130-200	80-110	140/100	[illegible]	0	[illegible], nif, [illegible], HCTZ		Short term problem early; Moved from 2 to 4	1
43-1020	1	0	0	150/80	125-160	70-100	140/85	dicl	1	[illegible], capto			1
43-1030	0	1	0	150/90	150-185	80-100	150/90	dicl	1	nif		Not aggressively controlled	0
44-1005	0	1	0	160/90	135-200	78-120	140/80	[illegible]	1	nif to enalapril		One spike in BP	1
5-1002	0	1	0	176/84	150-154	80-100	150/88	[illegible]	0	0		mild HTN during study, not treated	1
5-1003	0	0	albuminuria	130/75	125-148	77-100	140/84	ketoprofen	1	0		mild HTN during study, not treated	1
52-1002	0	0	0	110/80	120-150	70-100	120/80	dicl	0	0		Settled to 150/80	1
55-1006	0	1	0	150/98	135-170	80-110	185/120	naproxen to ketoprofen	0	[illegible]			1
56-1001	0	1	0	150/95	140-170	90-115	160/95	[illegible]	0	nif & [illegible]			1
57-1013	0	1	0	170/80	140-210	80-100	160/90	[illegible]	0	enalapril			1
58-1006	1	1	0	180/140	143-190	80-100	150/100	[illegible]	0	enalapril			1
58-1009	1	1	0	160-95	130-160	78-95	150/90	0	0	[illegible]			1
58-1012	0	0	0	140/95	140-190	88-120	150/90	0	0	enalapril			0
58-1017	0	1	0	200/88	122-176	74-100	160/70	0	0	enalapril			1
58-1020	0	1	albuminuria	160/97	150-200	88-85	160/80	dicl	0	enalapril, [illegible]		increased dose	1
62-1003	1	1	0	160/90	130-200	80-120	170/100	dicl	1	[illegible]			1
70-1012	1	0	0	160/80	130-190	80-96	180/98	ketoprofen	0	nif			1
72-1003	1	1	0	160/100	145-190	80-115	150/80	0	1	[illegible], nif, [illegible]		increased and added meds	1
72-1008	0	1	0	150/90	130-160	70-110	150/95	0	0	nif			1
76-1005	0	0	0	140/80	120-180	70-95	145/80	dicl	1	0			1
76-1008	0	1	0	150/90	120-150	70-90	160/100	[illegible]	1	0			1
6-1007	0	1	0	175/95	140-210	88-120	185/100	dicl	1	[illegible]		not aggressively treated	0
83-1004	0	1	0	160/90	132-165	63-114	140/80	[illegible]	1	0			1
85-1002	0	0	0	130/90	130-180	78-110	135/80	[illegible]	0	[illegible], spironolactone			1
88-1014	0	1	edema, [illegible]	156/90	140-290	85-105	160/105	naproxen	0	hctz			1
95-1003	1	1	0	200/100	145-200	80-120	165/80	[illegible]	0	nif		increased dose of nif	1
96-1001	0		0	160/90	120-180	60-110	150/90	dicl	0	0			1
C. 301US													
1-8	0	0	0	160/80	130-160	70-82	178/70	[illegible]	0	[illegible]			1
10-3	0	1	edema [illegible]	153/82	122-142	78-80	150/80	naproxen	0	vasotec			1
11-6	1	1	0	150/90	124-176	80-98	124/84	[illegible]	0	[illegible], [illegible]			1
17-6	1	1	0	140/88	128-160	62-88	132/82	dicl	0	hctz			1
17-7	1	0	edema, [illegible]	150/88	140-176	86-110	154/82	daypro	1	procardia, [illegible], dyazide		increased dose of procardia	1
18-2	0	0	0	145/80	135-160	80-100	142/80	dicl	0	vasotec			1
20-11	0	0	0	150/80	124-160	70-100	130/76	daypro	1	vasotec		increased dose of vasotec	1
21-11	1	0	0	122/80	240	160	164/84	[illegible]	0	nif, [illegible]		early discontinuation	1
22-11	0	0	0	122/80	130-160	70-86	146/90	[illegible]	0	vasotec, [illegible]			1
22-3	0	1	0	154/86	132-160	82-112	160/97	[illegible]	0	[illegible], [illegible]			1
23-23	1	0	0	130/84	132-160	68-88	172/110	0	1	procardia XL, [illegible]			1
23-24	0	1	0	172/82	120-170	78-84	150/84	[illegible]	1	[illegible]			1
25-2	1	0	0	130/80	128-164	80-100	145/88	[illegible]	1	procardia, [illegible]		increased dose of procardia	1
26-5	1	1	0	160/90	140-188	70-82	140/72	[illegible]	1	norvasc, [illegible]		increased dose of norvasc	1
32-18	1	0	0	174/84	110-150	68-80	158/100	naproxen	1	calan SR		increased dose of calan	1
32-20	1	0	0	154/82	130-168	80-112	154/77	daypro	1	dyazide, calan			1
32-4	0	1	albuminuria	150/82	120-158	92-116	158/116	[illegible]	1	dyazide, calan			1
47-16	1	1	0	170/88	152-190	82-100	160/84	[illegible]	0	[illegible], hctz, [illegible]			1
54-4	0	0	0	140/80	124-160	76-88	136/86	dicl	1	[illegible]			1
54-9	0	0	0	130/86	120-180	70-80	140/100	[illegible]	0	dyazide			1

Footnotes:
Elevated BP at Baseline = the highest of [illegible] days Prior to Baseline or Baseline
Elevated BP at Baseline >= 150/90 (must be elevated for SBP and DBP) else 1 = Yes and 0 = No
Endpoint = last time on drug
Determination of "Controlled" is confounded by not knowing prior BP variability. 1 = Yes controlled during study, 0 = no not controlled well

Table 3 Summary of Patients with Allergic Reactions as an Adverse Event														
	LEF all RA Studies		Placebo-Controlled Studies: US301 & MN301								Active Control Study: MN302			
			LEF		PL		MN301/3 SSZ		US301 MTX		MTX		LEF	
Criteria	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total Patients	1339		315		210		133		182		498		501	
Occurrence	218	16.3	68	21.6	25	11.9	23	17.3	31	17.0	72	14.5	94	18.8
AE	216	16.1	68	21.6	25	11.9	22	16.5	31	17.0	72	14.5	93	18.6
SAE	2	0.1	0	0.0	0	0.0	1	0.8	0	0.0	0	0.0	1	0.2
Study Treatment														
Discontinued			9	2.9	6	2.9	6	4.5	1	0.5	1	0.2	5	1.0
Duration														
Mean	42.85		26.22		31.59		47.53		17.52		32.13		64.59	
2 days or less	7	0.5	4	1.3	0	0.0	0	0.0	4	2.2	7	1.4	3	0.6
3 to 7 days	20	1.5	8	2.5	3	1.4	5	3.8	3	1.6	5	1.0	5	1.0
8 to 28 days	58	4.3	21	6.7	9	4.3	5	3.8	12	6.6	22	4.4	16	3.2
Greater than 28 days	90	6.7	23	7.3	6	2.9	5	3.8	8	4.4	17	3.4	49	9.8
Severity														
Mild	122	9.1	41	13.0	20	9.5	12	9.0	22	12.1	56	11.2	58	11.6
Moderate	82	6.1	21	6.7	4	1.9	9	6.8	8	4.4	14	2.8	31	6.2
Severe	13	1.0	5	1.6	1	0.5	2	1.5	1	0.5	2	0.4	5	1.0
Relatedness														
Not Related	61	4.6	23	7.3	11	5.2	1	0.8	19	10.4	34	6.8	29	5.8
Possibly Related	149	11.1	38	12.1	12	5.7	22	16.5	12	6.6	38	7.6	65	13.0
Probably Related	7	0.5	6	1.9	2	1.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 3 Summary of Patients with Allergic Reactions as an Adverse Event

Criteria	LEF all RA Studies		Placebo-Controlled Studies: US301 & MN301								Active Control Study: MN302			
			LEF		PL		MN301/3 SSZ		US301 MTX		MTX		LEF	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Treatment														
None	19	1.4	17	5.4	8	3.8	0	0.0	15	8.2	0	0.0	0	0.0
Drugs/Therapy	199	14.9	51	16.2	17	8.1	23	17.3	15	8.2	72	14.5	94	18.8
Outcome														
Resolved	174	13.0	55	17.5	18	8.6	14	10.5	26	14.3	55	11.0	70	14.0
Resolved w/Sequelae	1	0.1	1	0.3	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0
Continuing	43	3.2	12	3.8	7	3.3	9	6.8	4	2.2	17	3.4	24	4.8
Cumulative Incidence (KMA%)														
1 month or less		--		6.4		2.9		2.3		3.9				
3 months or less		--		18.0		9.5		11.9		11.3				
6 months or less		--		23.4		12.6		17.0		12.0				
9 months or less		--		25.9		15.9		19.4		16.0				
12 months or less		--		26.8		18.1		21.3		21.9				

REF: Appendix Tables 67.1, 67.2, and 385; US301 Study Report p. 142-143; MN302 Study Report Tables 100, 101.

Table 16 Summary of Patients with Infection (Grouped) as an Adverse Event														
	LEF all RA Studies		Placebo-Controlled Studies: US301 & MN301								Active Control Study: MN302			
			LEF		PL		MN301/3 SSZ		US301 MTX		MTX		LEF	
Criteria	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total Patients	1339		315		210		133		182		498		501	
Occurrence	533	39.8	140	44.4	81	38.6	50	37.6	109	59.9	237	47.6	235	46.9
AE	516	38.5	135	42.9	80	38.1	48	36.1	108	59.3	229	46.0	229	45.7
SAE	38	2.8	9	2.9	2	1.0	2	1.5	2	1.1	15	3.0	18	3.6
Study Treatment														
Discontinued	21	1.6	5	1.6	2	1.0	2	1.5	2	1.1	8	1.6	9	1.8
Duration														
Mean	20.7		19.02		16.73		16.39		19.1		25.71		25.78	
2 days or less	10	0.7	2	0.6	0	0.0	1	0.8	3	1.6	6	1.2	6	1.2
3 to 7 days	74	5.5	21	6.7	9	4.3	9	6.8	14	7.7	20	4.0	24	4.8
8 to 28 days	220	16.4	62	19.7	40	19.0	26	19.5	42	23.1	110	22.1	84	16.8
Greater than 28 days	201	15.0	49	15.6	24	11.4	10	7.5	45	24.7	90	18.1	106	21.2
Severity														
Mild	207	15.5	64	20.3	45	21.4	29	21.8	56	30.8	100	20.1	101	20.2
Moderate	279	20.8	65	20.6	31	14.8	17	12.8	48	26.4	111	22.3	119	23.8
Severe	43	3.2	11	3.5	5	2.4	4	3.0	5	2.7	26	5.2	15	3.0
Relatedness														
Not Related	413	30.8	114	36.2	71	33.8	39	29.3	97	53.3	156	31.3	163	32.5
Possibly Related	113	8.4	26	8.3	9	4.3	11	8.3	12	6.6	81	16.3	71	14.2
Probably Related	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Memo re. NDA 20-905 - Leflunomide
Date: August 27, 1998

The Four Month Safety Update Report has been sent in by the sponsor and reviewed by me. The updated figures for malignancies and other serious events were not materially different, and the current numbers are reflected in my review and in the label, where appropriate. Similarly, the overall adverse event and laboratory profiles, submittted on August 3, 1998, as additional information to that report, did not reveal any new "signals", ie. an unexpected excess in any adverse events, compared to controls.

Kent Johnson, M.D. 8/27/98
Medical Officer

JEH 9-3-98

cc:
NDA 20-905
D-550 D.V. F:6
HFD-550/Johnson
HFD-550/Cook