

g. Data showing comparability of groups at baseline  
(Tables 9 and 10)

As mentioned above, a total of 180 patients with biopsy-proven PBC were randomized into two experimental groups. As shown in Table 9, the two groups were similar and there were no statistically significant differences in demographic characteristics. These include the number of patients randomized per group (UDCA, n=89; PL, n=91), gender (most patients were women (UDCA=92%; PL=87%)), mean age (UDCA=54y; PL=52y) and height. Distribution of occupational status (data not shown) was also comparable between the two groups. The groups were also similar in the distribution of associated diseases (active medical problems other than PBC) and with regard to pharmacologic treatment taken 3 months prior to randomization into the trial. Individually, the medications most often taken had been Questran (UDCA=23%; PL=30%), steroids (UDCA=17%; PL=15%), D-Penicillamine (UDCA=13%; PL=9%), colchicine (UDCA=7%; PL=12%) and cyclosporine (UDCA=3%; PL=5%).

A summary of the disease characteristics at baseline is given in Table 10. The treatment groups were reasonably balanced with regards to these variables. The mean duration of PBC diagnosis was 39 months for UDCA patients and 44 months for those randomized to PL. The number of patients with jaundice at entry was the same at each group (n=11). In the UDCA group, the number of patients with total serum BIL  $\geq 2.5$  mg/dl at entry was 18; this number was very similar to the corresponding number in the PL group (n=16). Forty-seven patients in the UDCA group and 45 in the PL group had pruritus at baseline, with a mean duration of 37 and 45 months, respectively, and a mean of 0.8 (both Tx groups). Twelve patients in the UDCA group and 13 in the PL group had fatigue at baseline, with a mean duration of 24 and 31 months, respectively.

The groups were well-balanced with regards to hepatic biochemical markers. On the average, UDCA had 0.8 mg/dl of serum BIL higher than the ULN and this compared to 0.7 mg/dl for PL. Serum AP was  $>1000$  IU/l higher (more than x5) than the ULN (both groups). SGOT was more than x3 ULN (both groups). PT was close to the upper limit of normal (both groups) and very similar in the two experimental groups. Albumin was slightly decreased (UDCA = -0.1; PL = -0.2 mg/dl) when compared to the normal values at the Mayo Clinic.

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**TABLE 9**  
Mayo Clinic Trial

Data Showing Comparability of Groups at Baseline

	UDCA (n=89)	PL (n=91)	p-value
<b>A. DEMOGRAPHICS</b>			
No. of Pts. Randomized	89	91	
SEX (No. & F)	82 (92%)	79 (87%)	N.S.
MEAN AGE (y)	54	52	N.S.
MEAN HEIGHT (cm)	163	164	N.S.
<b>B. ASSOCIATED DISEASES (%)</b>			
Arthritis	7.9	9.9	N.S.
Breast Cancer	1.1	1.1	
Cholelithiasis	23.6	18.7	
CAH	0	0	
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Hyperthyroid	0	1.1	
Lymphoma	0	0	
Myxedema	1.1	3.4	
Osteodystrophy	3.4	3.3	
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Osteoporosis	14.8	10.1	
Pancreatitis	1.1	0	
Raynaud's Syndrome	5.6	13.2	
Renal Stones	4.6	2.3	
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Renal Tubular Acidosis	0	1.2	
Scleroderma	1.1	3.3	
Sicca Syndrome	33.3	26.4	
Sjögren's Syndrome	11.2	11.0	
Thyroid Hashimoto	9.0	4.5	
<b>C. PHARMACOLOGIC TREATMENT 3 MONTHS PRIOR TO RANDOMIZATION INTO TRIAL</b>			
Questran	21 (23%)	27 (30%)	N.S.
Steroids	15 (17%)	14 (15%)	N.S.
D-Penicillamine	12 (13%)	8 (9%)	N.S.
Colchicine	6 (7%)	11 (12%)	N.S.
Cyclosporine	3 (3%)	5 (5%)	N.S.
Azathioprine	2 (2%)	1 (1%)	N.S.
Barbiturates	1 (1%)	1 (1%)	N.S.
Other Drugs	41 (47%)	52 (57%)	N.S.
Drug Allergy	27 (30%)	37 (41%)	N.S.

**TABLE 10**  
Mayo Clinic Trial

Comparison of Disease Baseline Characteristics

		UDCA [n=89]	PL [n=91]	p-value
<b>A. Symptoms/Disease Duration</b>				
Mean Duration of PBC Dx (months)		39 (±52)	44 (±55)	N.S.
<b>JAUNDICE</b>				
No. of Pts. with		11	11	N.S.
No. of Pts. with BIL ≥2.5 mg/dl		18	16	N.S.
<b>PRURITUS</b>				
No. of Pts. with		47	48	N.S.
Mean Duration of (months)		37 (±38)	45 (±38)	N.S.
Mean		0.8	0.8	N.S.
<b>FATIGUE</b>				
No. of Pts. with		12	13	
Mean Duration of (months)		24 (±29)	31 (±27)	
Mean		1.0	0.9	N.S.
<b>B. Hepatic Biochemical Markers</b>				
Mean	Normal Value/Units			
Total BIL	0.1-1.1 (mg/dl)	1.86	1.76	N.S.
AP	90-234 (IU/l)	1334	1256	N.S.
SGOT	12-31 (IU/l)	99.4	97.5	N.S.
PT	8.4-12 (sec)	11.8 [n=87]	11.6 [n=90]	N.S.
Albumin	3.5-5.0 (g/dl)	3.4	3.3	N.S.
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<b>AMA<sub>s</sub></b>		2810.6 [n=87]	3206.6 [n=91]	N.S.
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<b>IMMUNOGLOBULINS</b>				
IgM	60-400	675.9 [n=82]	491.6 [n=82]	0.0019
IgA	60-300	272.2 [n=82]	298.0 [n=82]	N.S.
IgG	700-1500	1619.8 [n=82]	1710.1 [n=82]	N.S.
γ-GLOBULIN	0.7-1.7 (g/dl)	1.9 [n=87]	1.9 [n=90]	N.S.
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<b>BILE ACIDS IN DUODENAL CONTENTS</b>				
UDCA	‡	1.4 [n=78]	1.4 [n=80]	N.S.
CA	‡	54.2 [n=78]	54.2 [n=79]	N.S.
CDCA	‡	32.2 [n=78]	33.5 [n=79]	N.S.
DCA	‡	10.4 [n=78]	10.2 [n=77]	N.S.
LCA	‡	0.18 [n=78]	0.35 [n=77]	N.S.
Sulfa-LCA	‡	0.36 [n=78]	0.29 [n=77]	N.S.

TABLE 10 (Con't)

C. Presence of Esophageal Varices			
YES	18 (19%)	22 (23%)	N.S.
D. Mayo Risk Score			
n	87	90	
Median	5.0	4.8	N.S.
Mean	5.1	5.0	
Range	2.9 to 7.8	2.9 to 8.8	
E. Hepatic Histology			
<u>MEAN</u>			
Stage of Disease	2.9 [n=86]	3.0 [n=87]	N.S.
Copper Stain	1.0 [n=62]	1.1 [n=61]	N.S.
Bile Stasis	0.2 [n=82]	0.2 [n=85]	N.S.
Fibrosis	1.6 [n=78]	1.8 [n=75]	N.S.
<u>INFLAMMATION</u>			
• Overall	1.4 [n=81]	1.5 [n=80]	N.S.
• Portal	1.5 [n=82]	1.6 [n=82]	N.S.
• Periportal	1.4 [n=84]	1.5 [n=83]	N.S.
• Lobular	0.5 [n=81]	0.7 [n=80]	N.S.
• Other	0.6 [n=69]	0.7 [n=71]	N.S.
<u>DISTRIBUTION OF HISTOLOGIC STAGE</u>			
I	7 (8%)	3 (3%)	N.S. (all stages)
II	23 (27%)	22 (25%)	
III	31 (36%)	36 (41%)	
IV	25 (29%)	26 (30%)	
F. Etiological Factors			
Family History Liver Disease	11 (13%)	11 (12%)	N.S.
History of Hepatitis	15 (17%)	9 (10%)	N.S.
Past Use of Alcohol	29 (33%)	29 (33%)	N.S.
Social Excess	3 (3%)	2 (2%)	N.S.
Present Use of Alcohol	12 (13%)	9 (10%)	N.S.
Child-Bearing Age Female*	20 (22%)	29 (32%)	N.S.
Post-menopausal	34 (38%)	33 (36%)	N.S.
Hysterectomy	29 (33%)	18 (20%)	N.S.
Phenothiazine	1 (1%)	0 (0%)	N.S.
Estrogen	23 (26%)	19 (21%)	N.S.
Oral Contraceptives	21 (24%)	21 (23%)	N.S.
G. Surgical History			
Portal Shunt	0	3 (3%)	N.S.
Cholecystectomy	14 (16%)	14 (15%)	N.S.
Other Abd. Surgery	37 (42%)	38 (42%)	N.S.
Mastectomy	2 (2%)	4 (4%)	N.S.
Other Surgery	40 (45%)	43 (47%)	N.S.
a) Not including patients with hysterectomies			

Biochemical markers of liver disease also include immunologic parameters (Table 10). The two treatment groups were well-balanced with respect to AMA<sub>s</sub> (normal=zero; UDCA=2811, PL=3207), IgA, IgG and  $\gamma$ -globulin. However, the baseline IgM antibody titer was significantly different between the two treatment groups (UDCA=676, PL=492,  $p < 0.05$ ). The upper limit of IgM in the Mayo Clinic is 300. By this parameter, the UDCA treatment group appeared to have more disease than did the PL group.

The proportion (%) of the various BAs in duodenal contents was very similar between the two treatment groups (Table 10). As expected, at baseline and percentage-wise, the predominant bile acid was CA (54%) followed by CDCA (ca. 33%) and DCA (10%). Pre-Treatment, the proportion of UDCA was low (1.4%) and that of LCA even lower (UDCA=0.18%, PL=0.35%). Also, as expected, most of the LCA present appeared to be sulfated.

At baseline, there was no statistically significant difference in the proportion of patients who had already developed esophageal varices (UDCA=18/89=19%; PL=22/91=23%) or in the mean (UDCA=5.1; PL=5.0) or median (UDCA=5.0; PL=4.8) Mayo risk score (Table 10). As shown in this Table the two treatment groups were reasonably balanced with respect to hepatic histologic parameters. The distribution of histologic stage was also similar between the two treatment groups. At baseline, for both groups, the proportion of patients in stage I was lower (UDCA=8%; PL=3%) than the corresponding proportion of patients in stages II, III or IV.

Finally, the groups were reasonably balanced in terms of etiologic factors for hepatic disease and surgical histories for complications of PBC as well as other surgeries (Table 10). Of the etiologic factor for liver disease, none of the patients in the two treatment groups had been exposed to arsenicals, methyl testosterone or cholestatic drugs.

In conclusion, in the Mayo Clinic trial, the two treatment groups were comparable to each other at baseline. Comparability between the two experimental groups was shown with respect to demographics, associated diseases, pharmacologic treatment 3 months prior to randomization into trial, symptoms/disease duration, presence of esophageal varices, Mayo Risk Score, hepatic histology, etiological factors for liver disease and surgical histories for complications of PBC and other surgeries. Hepatic biochemical parameters (including AMA<sub>s</sub>), % of BAs in duodenal contents and, except for IgM, Immunoglobulins, were also similar between the two groups at baseline. The exception was IgM. This immunologic parameter was statistically significantly higher in the UDCA than in the PL group. This imbalance appears to suggest that the patients in the UDCA group had more disease, and may be weighted against this group. However, the so many other parameters of evaluation showed that the two treatment groups were well-balanced in comparison to each other.

h. Efficacy Results

Introductory Note - During the assessment of efficacy the reviewer emphasizes therapeutic gain: clinically important favorable effects ( $\Delta$  = UDCA - PL) on the different clinical/biochemical parameters of evaluation carried out to fulfill the specific aims listed in the protocol. In statistical evaluations, differences in change from baseline to at least 24 months of treatment or endpoint between the two treatment groups, are compared.]

1) Summary of treatment failures (Table 11)

In the UDCA group, 20 patients (or 23%) failed. This proportion of patients failing was statistically significantly lower than the 40 patients (or 47%), representing a therapeutic gain of 24%.

**TABLE 11**  
Mayo Clinic Trial

## Summary of Treatment Failures

	UDCA [n=86] <sup>a</sup>	PL [n=86] <sup>b</sup>	Therapeutic Gain	p-value <sup>c</sup>
YES [n=60]	20 (23%)	40 (47%)	24%	<0.01
NO [n=112]	66 (77%)	46 (53%)		
a) 3 patients completed only the baseline visit b) 5 patients completed only the baseline visit c) Fisher's Exact Test				

2) Reason for treatment failure at the last visit/  
first reason for treatment failure (Table 12)

This Table shows the actual reasons for treatment failure. With a therapeutic gain of 11%, doubling of BIL was the only reason for treatment failure at the last visit where the difference between UDCA and PL was statistically significant (p=0.01). Doubling of total BIL was also the only first reason for treatment failure where the therapeutic gain (12%) was statistically significant (p=0.01). The therapeutic gain for other reasons for treatment failure (ex. 4% less deaths, 5% less voluntary withdrawals, 5% less development of ascites) was lower and, in some instances (ex. 1% less development of PSE or 1% less histologic progression), of little clinical significance.

At the Mayo Clinic, one of the traditional reasons for treatment failure is drug toxicity. As seen in Table 12, no patients in either group were D/C from the trial for drug toxicity.

**TABLE 12**  
**Mayo Clinic Trial**  
**Reasons for Treatment Failure**

Reason at Last Visit <sup>a</sup>					First Reason <sup>b</sup>			
Reason for Treatment Failure	UDCA n (%)	PL n (%)	Therapeutic Gain	p-value <sup>c</sup>	UDCA n (%)	PL n (%)	Therapeutic Gain	p-value <sup>d</sup>
Drug Toxicity	0	0	---	---	0	0	---	---
Death	3 (3)	6 (7)	- 4%	N.S.	2 (2)	6 (7)	- 5%	N.S.
Voluntary W/D	6 (7)	11 (13)	- 6%	N.S.	6 (7)	10 (12)	- 5%	N.S.
Transplantation	3 (3)	5 (6)	- 3%	N.S.	3 (3)	4 (5)	- 2%	N.S.
Total BIL x 2	2 (2)	11 (13)	-11%	0.01	2 (2)	12 (14)	-12%	0.01
Worse Symptoms	2 (2)	2 (2)	0%	---	3 (3)	2 (2)	NONE	N.S.
Develop. Varices	6 (7)	8 (9)	- 2%	N.S.	6 (7)	5 (6)	NONE	N.S.
Develop. Ascites	0	4 (5)	- 5%	N.S.	0	4 (5)	- 5%	N.S.
Develop. PSE	0	1 (1)	- 1%	N.S.	0	1 (1)	- 1%	N.S.
Histol. Progress	6 (7)	7 (8)	- 1%	N.S.	5 (6)	6 (7)	- 1%	N.S.

• A breakdown by patient, of the reasons for treatment failures was provided by sponsor in their Appendix H.

a) In this Table, patients are counted more than once if, at the last visit, they were classified as treatment failures for more than one reason.

b) Patients are counted more than once if they were classified as treatment failures for more than one reason.

c and d) Fisher's Exact Test

### 3) Time to treatment failure (Table 13)

As shown, the time to treatment failure in the UDCA group was, on the average, ca. 163 days longer than the time to treatment failure in the PL group. This therapeutic gain of ca. >5 mo. was statistically significant.

- Also examined was the quartile distribution of time to Tx Fx. The results were presented in sponsor's Table J (not shown): at each quartile, time to Tx Fx was longer by 3 months or more for the UDCA group than the PL group.

**TABLE 13**  
Mayo Clinic Trial

Mean Time (Days) to Treatment Failure <sup>a,b</sup>

	UDCA <sup>c</sup> [n=86]	PL [n=86]	Therapeutic Gain (days)	p-value <sup>c</sup>
	804 (±25) <sup>d</sup>	641 (±24) <sup>e</sup>	163	0.0001
Number Failed [n=60]	20	40		

a) 24-month nominal visit. Calculated by Life Table Analysis at Two Years.  
 b) The incidence of treatment failure over time was shown in sponsor's Fig. A.  
 c) Log rank test.  
 d, e) S.E. of the Mean

4) Time to treatment failure stratified by bilirubin at baseline (Table 14)

- For patients in the stratum with BL total serum BIL of  $\leq 1.8$  mg/dl, the mean time to treatment failure in the UDCA group was, on the average, 166 days longer than the time to Tx Fx in the PL group. This therapeutic gain of ca. >5 months was statistically significant.
- For patients in the stratum with BL total serum BIL >1.8 mg/dl, the time to treatment failure in the UDCA group was, on the average, 124 days longer than the time to Tx Fx in the PL group. This therapeutic gain of ca. 4 months was statistically significant (p=0.01) using the Log rank test. But this statistical significance was not corroborated when the results in this stratum were analyzed using the Wilcoxon test (p=0.06).
- Nonetheless, when the quartile distribution of time to Tx Fx was examined (data not shown), time to Tx Fx was consistently longer for the UDCA group than the PL group

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TABLE 14  
Mayo Clinic Trial

Mean Time (Days) to Treatment Failure  
Stratified by BIL at Baseline

Baseline Total BIL		UDCA	PL	Therapeutic Gain (days)	p-value
≤ 1.8 mg/dl		[n=65]	[n=63]		
	Mean	822 (±27) <sup>a</sup>	656 (±29) <sup>b</sup>	166	0.003 <sup>c</sup>
	No. of Failures [n=38]	14	24		
> 1.8 mg/dl		[n=21]	[n=23]		
	Mean	737 (±43) <sup>c</sup>	613 (±45) <sup>d</sup>	124	0.01 <sup>e</sup> , 0.06 <sup>f</sup>
	No. of Failures [n=22]	6	16		
a,b,c and d) S.E. of the Mean e,f) Log rank test g) Wilcoxon test					

5) Time to treatment failure stratified by histologic stage at baseline (Table 15)

- Time to Tx Fx was stratified by BL histologic stages I, II, III and IV, separately.
  - For stages II and III respectively, mean time to Tx Fx was significantly longer in the UDCA than the PL groups (p<0.01).
  - But for stages I and IV respectively, mean time to Tx Fx was not significantly different between the two treatment groups (p>0.05).
- The results were examined on the basis of whether the patients had early (stages I and II combined) or late (stages III and IV combined) histologic stage at BL. Of the 13 patients that failed in the I+II BL stage stratum, 9 had received PL and 4 were given UDCA. In this stratum of patients, the mean time to Tx Fx in the UDCA was, on the average, 80 days longer than the mean time to Tx Fx in the PL group and this therapeutic gain was statistically significant (p=0.02).

Of the 42 patients that failed in the III + IV BL stage stratum, 29 had received PL and 13 UDCA. In this stratum of patients, the mean time to Tx Fx in the UDCA was, on the average, 180 days longer than the mean time to Tx Fx in the PL group and this therapeutic gain of nearly 6 months, was statistically significant (p=0.0003).

TABLE 15  
Mayo Clinic Trial

Mean Time to Treatment Failure Stratified by  
Histologic Stage at Baseline

Baseline Total BIL		UDCA	PL	Therapeutic Gain (days)	p-value*
I & II		[n=29]	[n=23]		
	Mean	756 (±33) <sup>a</sup>	676 (±43) <sup>b</sup>	80	0.02
	No. of Failures [n=13]	4	9		
III & IV		[n=54]	[n=59]		
	Mean	805 (±32) <sup>c</sup>	625 (±31) <sup>d</sup>	180	0.0003
	No. of Failures [n=42]	13	29		

a, b, c and d) S.E. of the Mean  
e) Log rank test

6) Time to treatment failure stratified by baseline BIL together with baseline histologic stage

Baseline BIL and baseline histologic stage were entered into the Cox's proportional hazard model and logistic regression analyses were performed. Treatment failure was still statistically significant in favor of the UDCA-treated group ( $p < 0.001$ ).

7) Effect on survival or need for transplantation (Table 16)

- Data at two years (Life Table analysis) (upper panel of Table 16) showed 11 PL failing, in comparison to 6 in the UDCA group. There was no therapeutic gain and no significant difference in the time to death and/or transplant between the two treatment groups.
- As seen in the middle panel of Table 16, there was a therapeutic gain of 256 days (UDCA better than PL) with respect to the time to death and/or transplant in the stratum of patients with  $\leq 1.8$  mg/dl BIL at baseline. But this therapeutic gain was not statistically significant. In the stratum of patients with  $> 1.8$  mg/dl BIL at baseline, there was no significant difference between the treatment groups in mean time to death and/or transplant.

- As shown in the lower panel of Table 16, there was no significant difference noted for the time to death and/or transplant when stratified by histologic stage ("early" = I & II vs "late"=III & IV).
  - Results for BL stages I, II, III and IV separately also did not reveal any statistically significant difference in time to death and/or transplant between the two treatment groups.
- The sponsor also carried out covariance analysis using death and/or transplants as response and total BIL at BL and histologic stage at BL as covariates. Cox's and logistic models were used for these analyses. The conclusions did not change appreciably. There was no significant difference ( $p > 0.05$ ) between the treatment groups.

**TABLE 16**  
Mayo Clinic Trial

Effect on Survival or Need for Transplantation

A. Life Table Analysis at Two Years					
		UDCA	PL	Therapeutic Gain (days)	p-value <sup>b</sup>
Time to Treatment Failure (days)		[n=86]	[n=86]		
	Mean	707 (±10) <sup>a</sup>	732 (±19)	NONE	N.S.
	Number Failed [n=17]	6	11		
B. Stratified by Bilirubin at Baseline					
Baseline Total Bilirubin (mg/dl) ≤ 1.8		[n=65]	[n=63]		
	Mean	708 (±13)	452 (±8)	256	N.S.
	Number of Death/Transplants [n=8]	4	4		
> 1.8		[n=21]	[n=23]		
	Mean	624 (±13)	682 (±45)	NONE	N.S.
	Number of Death/Transplants [n=9]	2	7		
C. Stratified by Histologic Stage at Baseline					
Baseline Histologic Stage I & II		[n=29]	[n=21]		
	Mean	No Estimate	463 (±6)	N/E	N/A
	Number of Death/Transplants [n=2]	0	2		
III & IV		[n=54]	[n=59]		
	Mean	615 (±12)	729 (±24)	NONE	N.S.
	Number of Death/Transplants [n=12]	4	8		

a) ± SE Mean  
b) Log rank test  
N/E = Not Evaluated                      N/A = Not Applicable

- It is to be noted that in all groups and subgroups, there was a low number of events of death and/or transplant:

8) Effects on symptoms (Table 17)

- At baseline, both treatment groups were similar with respect to pruritus and fatigue (Table 10). To facilitate comparisons, these baseline data are repeated in Table 17.
- There was a statistically significant decrease from baseline in fatigue (but not in pruritus) in the UDCA group, but not in the PL group. The differences in change to endpoint from BL in pruritus and fatigue were not significantly different between the two treatment groups.

**TABLE 17**  
Mayo Clinic Trial

Summary of Changes in Symptoms from Baseline

Symptom		Baseline		Endpoint		Change from Baseline		p-value
		UDCA	PL	UDCA	PL	UDCA	PL	
Pruritus		[n=89]	[n=91]	[n=83]	[n=76]	[n=83]	[n=76]	N.S.
	Mean (± SD)	0.8 (±0.8)	0.8 (±0.9)	0.6 (±0.7)	0.9 (±0.8)	-0.2 (±0.8)	0.01 (±0.8)	
Fatigue		[n=89]	[n=91]	[n=83]	[n=76]	[n=83]	[n=76]	N.S.
	Mean (± SD)	1.0 (±0.8)	0.9 (±0.8)	0.7 (±0.8)	0.9 (±0.8)	-0.3** (±0.9)	-0.03 (±1.0)	

\*\* Statistically different from zero,  $p < 0.01$ .

9) Effect on hepatic biochemical markers: change at endpoint from baseline (Table 18)

To facilitate comparisons, the reviewer is repeating the baseline data. These were presented in Table 10 (discussed above). It was noted that the two treatment groups were well-balanced with regard to hepatic biochemical markers and immunologic parameters, except IgM antibody titer. At baseline, the latter was significantly higher in the UDCA than in the PL treatment group.

- Except for ALB, all hepatic biochemical markers listed in Table 18 had improved considerably at endpoint, in comparison to baseline, in the group of patients treated with UDCA, but not in those treated with PL. These differences between UDCA vs PL were statistically significant. For ALB, a numerical improvement of UDCA over PL was not statistically significant. Also, as noted in the footnote to Table 18, when the corroboration of t-test was done using Wilcoxon test, the difference in change from BL to endpoint between the two treatment groups for IgA was borderline ( $p=0.06$ ).

- It is to be noted that UDCA's effect at endpoint is best described as a marked improvement, but not normalization of these hepatic biochemical markers (Table 18).

**TABLE 18**  
Mayo Clinic Trial

Hepatic Biochemical Markers: Change at Endpoint from Baseline\*

Parameter (Mean) (Normal Range)	BASELINE		ENDPOINT		CHANGE FROM BASELINE		p-value UDCA vs PL
	UDCA	PL	UDCA	PL	UDCA (± SD)	PL (± SD)	
Total BIL 0.1-1.1 (mg/dl)	1.86 [89]	1.76 [91]	1.27 [83]	2.29 [76]	-0.63** (1.8)	0.80** (1.86)	<0.0001
AP 90-234 (IU/l)	1334 [89]	1256 [91]	623 [83]	1260 [76]	-708** (691)	15 (563)	<0.0001
SGOT 12-31 (IU/l)	99.4 [89]	97.5 [91]	63.9 [83]	120.4 [76]	-36.2** (40.4)	25.5** (57.2)	<0.0001
PT 8.4-12 (sec)	11.8 [87]	11.6 [90]	11.7 [83]	11.9 [73]	-0.05 (1.08)	0.26* (0.85)	<0.05
ALB 3.5-5 (g/dl)	3.4 [89]	3.3 [91]	3.5 [83]	3.4 [76]	0.12* (0.49)	0.03 (0.49)	N.S.
IgM (60-400)	675.9* [82]	491.6 [82]	520.3 [83]	512.1 [75]	-151.9** (292.0)	31.8 (219.3)	<0.0001
IgA (60-300)	272.2 [82]	298.0 [82]	267.6 [83]	317.4 [75]	-1.1 (83.8)	26.2** (60.8)	<0.05 0.06 <sup>c</sup>
IgG (700-1500)	1619.8 [82]	1710.1 [82]	1526.8 [83]	1736.0 [75]	-94.0* (362.1)	59.6 (336.7)	<0.05
γ-Globulin 0.7-1.7 (g/dl)	1.9 [87]	1.9 [90]	1.9 [83]	2.0 [75]	-0.03 (0.58)	0.14** (0.41)	<0.05

\* Statistically significant from zero, p <0.05  
 \*\* Statistically different from zero, p <0.01  
 a) Depicted are rounded figures [to either one decimal point or no decimal].  
 b) UDCA statistically significantly higher than PL [p=0.0019]  
 c) This borderline statistical difference was obtained when the corroboration of t-test was done using Wilcoxon test.

10) Effects on cirrhosis, varices, ascites, portal systemic encephalopathy (Table 19)

- Patients randomized to UDCA stayed in the trial, on the average, 74 more days than those in the PL group. This difference was statistically significant.
- Although there were some numerical differences favoring UDCA over PL, there was no statistically significant difference between the two treatment groups in incidence of cirrhosis, development of varices, formation of ascites, spontaneous PSE or D/C from the trial.

**TABLE 19**  
Mayo Clinic Trial

Effects on Cirrhosis, Varices, Ascites, Portal Systemic Encephalopathy (PSE)

		UDCA	PL	THERAPEUTIC GAIN	p-value
Status Interval (days since randomization)	Mean	(n=86) 654 (± 171) <sup>a</sup>	(n=86) 580 (± 213) <sup>b</sup>	74 days	0.01
Cirrhosis	YES	22/67 (33%)	30/61 (49%)	-16%	N.S. <sup>c</sup>
	NO	45/67 (67%)	31/61 (51%)	16	
Develop Varices	YES	23/67 (34%)	28/62 (45%)	-11%	N.S.
	NO	44/67 (66%)	34/62 (55%)	11%	
Formation of Ascites	YES	4/85 (5%)	5/76 (7%)	-2%	N.S.
	NO	81/85 (95%)	71/76 (93%)	2%	
Spontaneous PSE	YES	0/85 (0%)	1/76 (1%)	-1%	N.S.
	NO	85/85 (100%)	75/76 (99%)	1%	
D/C from Study	YES	12/86 (14%)	23/86 (27%)	-13%	N.S. <sup>d</sup>
	NO	74/86 (86%)	63/86 (73%)	13%	
a,b) S.E. of the Mean c,d) Borderline at p-values of 0.07 and 0.06, respectively.					

11) Effects on liver biopsy findings (Tables 20, 21 and 22)

- At the endpoint of evaluation, most of the histopathological findings at baseline had not changed. Biopsy findings for cirrhosis from BL to end of study were not significantly different between the two treatment groups.

**TABLE 20**  
Mayo Clinic Trial

Biopsy Findings (Cirrhosis): Comparison of Baseline to Endpoint

		UDCA [n=58]	PL [n=41]	Therapeutic Gain	p-value
Biopsy Findings (Cirrhosis)	Same	45 (78%)	34 (83%)	-5%	N.S.
	YES → NO	6 (10%)	1 (2%)	8%	
	NO → YES	7 (12%)	6 (15%)	NONE	

- Details of the change from baseline in hepatic histology are given in Table 21. To facilitate comparisons, the data at BL (Table 10) are repeated in Table 21. According to the sponsor's calculations [their Table BD, vol. 35, page 103 (pagination with small numbers)], there was a significant increase from BL ( $p < 0.05$ ) in copper stain and significant ( $p < 0.05$ ) decrease in bile stasis in the UDCA group. In the PL group, stage of disease and copper stain both increased significantly ( $p < 0.05$ ) from baseline. For both groups, the changes in all five indices of inflammation and in fibrosis were minor and without statistical significance.
- As presented in Table 10, stage of disease at BL was not significantly different between the UDCA- and PL-treated groups. There was no significant difference in stage of disease at endpoint between the two treatment groups (Table 22, upper panel). In the lower panel of Table 22, the change at endpoint for every histological parameter (better, same or worse) is presented. There was no significant difference in change in histology between the two treatment groups with respect to any parameters of histology (Table 22, lower panel).

**TABLE 21**  
**Mayo Clinic Trial**

**Hepatic Histology: Change from Baseline**

MEAN	Baseline (Mean) <sup>a</sup>		Visit 24 (Mean) <sup>b</sup>		UDCA (± SD)	PL (± SD)
	UDCA	PL	UDCA	PL		
Stage of Disease	2.9 (n=86)	3.0 (n=87)	3.0 (n=57)	3.1 (n=43)	0.1 (0.7)	0.3 <sup>c</sup> (0.7)
Copper Stain	1.0 (n=62)	1.1 (n=61)	1.2 (n=51)	1.3 (n=38)	0.3 <sup>d</sup> (0.9)	0.3 <sup>e</sup> (0.7)
Bile Stasis	0.2 (n=82)	0.2 (n=85)	0.1 (n=57)	0.1 (n=42)	-0.2 <sup>f</sup> (0.6)	-0.1 (0.4)
Fibrosis	1.6 (n=78)	1.8 (n=75)	1.8 (n=56)	2.0 (n=41)	0.2 (1.0)	0.4 (1.0)
<b>INFLAMMATION</b>						
• Overall	1.4 (n=81)	1.5 (n=80)	1.4 (n=57)	1.3 (n=42)	-0.1 (0.8)	-0.1 (0.8)
• Portal	1.5 (n=82)	1.6 (n=82)	1.4 (n=57)	1.3 (n=42)	-0.1 (0.8)	-0.2 (0.8)
• Periportal	1.4 (n=84)	1.5 (n=83)	1.2 (n=57)	1.2 (n=42)	-0.2 (1.0)	-0.2 (1.0)
• Lobular	0.5 (n=81)	0.7 (n=80)	0.6 (n=57)	0.6 (n=42)	0.0 (0.9)	-0.1 (0.8)
• Other	0.6 (n=69)	0.7 (n=71)	0.6 (n=49)	0.6 (n=37)	0.03 (0.9)	0.1 (1.2)
a,b) Depicted is the mean at the specified time for the specified group. The SD mean has been deleted for clarity of presentation. c through f) Statistically significant from zero, p ≤ 0.05.						

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**TABLE 22**  
Mayo Clinic Trial  
Stage of Disease and Change in the Histological  
Parameters at Endpoint

A. Stage of Disease				
Stage of Disease at Endpoint		UDCA n (%)	PL n (%)	p-value
I		4 (11)	1 (2)	N.S.
II		9 (16)	7 (16)	
III		28 (49)	22 (51)	
IV		16 (28)	13 (30)	
B. Change in Histological Parameters				
Histological Parameters				
Stage of Disease	Same	32 (56)	25 (60)	N.S.
	Better	11 (19)	4 (10)	
	Worse	14 (25)	13 (30)	
Copper Stain	Same	20 (50)	18 (64)	N.S.
	Better	6 (15)	2 (7)	
	Worse	14 (35)	8 (29)	
Bile Stasis	Same	44 (81)	34 (85)	N.S.
	Better	8 (15)	5 (13)	
	Worse	2 (4)	1 (3)	
Fibrosis	Same	25 (49)	15 (44)	N.S.
	Better	10 (20)	5 (15)	
	Worse	16 (31)	14 (41)	
Inflammation				
• Overall	Same	25 (47)	17 (47)	N.S.
	Better	16 (30)	12 (33)	
	Worse	12 (23)	7 (19)	
• Portal	Same	27 (50)	17 (46)	N.S.
	Better	16 (30)	13 (35)	
	Worse	11 (20)	7 (19)	
• Periportal	Same	21 (38)	12 (31)	N.S.
	Better	22 (39)	17 (44)	
	Worse	13 (23)	10 (26)	
• Lobular	Same	24 (45)	16 (44)	N.S.
	Better	14 (26)	12 (33)	
	Worse	15 (28)	8 (22)	
• Other	Same	16 (43)	10 (34)	N.S.
	Better	9 (24)	9 (31)	
	Worse	12 (32)	10 (34)	

12) Change in ultrasound parameters from baseline

These data was presented in sponsor's Table BE. The changes in U/S examinations, rated as same; other; abnormal to negative and negative to abnormal, between the two treatment groups were not statistically significantly different. The U/S parameters evaluated included a) parenchymal Echo Texture (evaluated same, as abnormal → normal; and normal → abnormal); b) ascites; c) Vascular Patency; and d) Portal Hypertension. Parameters b, c and d were evaluated as same; NO → YES; and YES → NO. There was no significant difference in change in U/S parameters between the two treatment groups from BL.

13) Change in Mayo Risk Score from baseline  
(Table 23)

To facilitate comparisons, the baseline data (Table 10) are repeated here. As shown in Table 23, while there was a significant ( $p < 0.01$ ) decrease from BL in Mayo Risk Score in the UDCA group, there was a significant ( $p < 0.01$ ) increase from BL in Mayo Risk Score in the PL-treated group. The difference in change in Mayo score from BL to endpoint between the two treatment groups was highly significant ( $p = 0.0001$ ) in favor of the UDCA-treated group.

TABLE 23  
Mayo Clinic Trial

Change in Mayo Risk Score from Baseline

Baseline		Endpoint		Change from Baseline		Therapeutic Gain	p-value <sup>d</sup>
UDCA	PL	UDCA	PL	UDCA	PL		
5.1 <sup>a</sup> ±1.1	5.0 ±1.1	4.8 ±1.1	5.3 ±1.1	-0.3 <sup>b</sup> ±0.6	0.3 <sup>c</sup> ±0.7	0.5	0.0001
(n=87)	(n=90)	(n=83)	(n=73)	(n=82)	(n=72)		
The formula for calculation of the Main Risk Score is as follows: $0.871 \cdot \log(\text{BIL}) - 2.53 \cdot \log(\text{ALB}) + 0.039 \cdot \text{age} + 2.38 \cdot \log(\text{PT}) + 0.859 \cdot \text{edema score}$							
a) p = not significant UDCA versus PL b,c) Statistically different from zero, $p \leq 0.01$ . d) p-value column compares change in Mayo Risk Score to endpoint from BL between the UDCA and the PL groups.							

14) Change in biliary BAs from baseline (Table 24)

To facilitate comparisons, the BL data (Table 10) are repeated here.

- In the UDCA-treated group, there was a significant increase ( $p < 0.01$ ) in UDCA and LCA and significant decrease from BL in CA and CDCA.

- In the PL group, there was a significant increase from BL in UDCA (?) and significant decrease from BL in CDCA (?), at a p of <0.05.

TABLE 24  
Mayo Clinic Trial

Change from Baseline: Biliary Bile Acids

Mean Bile Acid	Baseline		Visit 24		UDCA (± SD)	PL (± SD)
	UDCA	PL	UDCA	PL		
UDCA	1.39 (n=78)	1.39 (n=80)	43.92 (n=61)	13.07 (n=57)	42.3** (20.4)	8.1** (19.5)
CA	54.15 (n=78)	54.17 (n=79)	27.53 (n=61)	47.15 (n=57)	-25.1** (19.9)	-1.4 (21.0)
CDCA	32.16 (n=78)	33.52 (n=79)	18.39 (n=61)	28.43 (n=57)	-13.2** (11.9)	-6.7** (12.7)
DCA	10.36 (n=78)	10.23 (n=77)	9.84 (n=61)	9.88 (n=57)	- 1.6 (15.2)	-0.3 (14.4)
LCA	0.18 (n=78)	0.35 (n=77)	0.80 (n=60)	0.36 (n=58)	0.51** (1.06)	-0.05 (1.11)
Sulfa-LCA	0.36 (n=78)	0.29 (n=77)	0.42 (n=61)	0.63 (n=58)	0.03 (0.89)	0.15 (1.26)

\*\* Statistically different from zero, p <0.01.

i. Results of safety evaluations

1) Adverse events (Table 25)

Described in this Table is the incidence of AEs in both treatment groups at 12 and 24 months. This information was taken from sponsor's Table 28 (vol. 35, p. 065). Terms under which no patient in any of the groups experienced those AEs have been deleted [flushing, hypertension and liver toxicity]. Similarly, deleted from this Table have been the terms nausea/vomiting, other toxicity and fever because only PL-treated patients and no UDCA-treated patients experienced these AEs.

As shown in the lower panel of Table 25, there was not significant difference between the two treatment groups in the overall proportion of patients experiencing AEs at 12 months. But, at the 24-month visit, the proportion of patients experiencing AEs in the UDCA group (9%) was statistically significantly higher than PL (0%) (p=0.002).

**TABLE 25**  
Mayo Clinic Trial

Incidence of AEs at 12 and 24 Months and Overall  
Proportion of Patients Experiencing AEs

AE	Visit at 12 Months <sup>a</sup>		Visit at 24 Months <sup>b</sup>	
	UDCA n (%)	PL n (%)	UDCA n (%)	PL n (%)
<b>A. Incidence of Individual AEs</b>				
Diarrhea	2 (2.35)	2 (2.56)	1 (1.32)	0
↑ Creatinine	0	0	1 (1.32)	0
↓ Blood Glucose	1 (1.18)	0	1 (1.32)	0
Leukopenia	0	0	2 (2.63)	0
Nausea/Vomiting	0	2 (2.60)	0	0
Other Toxicity	0	1 (1.30)	0	0
Peptic Ulcer	0	0	1 (1.32)	0
Skin Rash	0	0	2 (2.63)	0
Thrombocytopenia	1 (1.18)	2 (2.56)	1 (1.32)	0
<b>B. Overall Proportion<sup>c</sup> of Pts. Experiencing AEs</b>				
p-value for Treatment Group Comparison	4 (5)	8 (9) (N.S.)	9 (10)	0 (0) (0.002)
<p>a, b) There was no statistically significant difference in incidence of individual AEs at 12 or 24 months between the two treatment groups (p&gt;0.05).</p> <p>c) Overall, UDCA=13 (15%), PL=8 (9%), p=N.S.</p>				

## 2) Patient withdrawals

- A total of 35 patients were withdrawn from the trial following two years or less of exposure to test medication. The reasons for withdrawal and the distribution and identification of the individual patients W/D from each treatment group are given in Table 26.

TABLE 26  
Mayo Clinic Trial

Summary of Patient Withdrawal

	UDCA [n=89]	PL [n=91]
Death	3 (3%) [#746, #804, #819]	6 (7%) [#708, #752, #763, #784, #802, #844]
Transplant	3 (3%) [#728, #757, #852]	5 (5%) [#756, #765, #774, #808, #832]
Voluntary Basis	5 (6%) [#704, #706, #770, #816, #851]	11 (13%) [#718, #743, #766, #769, #772, #773, #814, #817, #822, #826, #853]
Other	1 (1%) [#753]	1 (1%) [#799]
Drug Toxicity	0	0
New and/or Unexpected Drug Toxicities	0	0
TOTAL	12 (13%)	23 (25%)

**NOTE:** In this Table, patients are counted only once. For instance, patient #804 who voluntarily W/D on 6/4/90 and died 11/16/90 is counted only once under the most serious of the two outcomes, i.e., death.

a) Withdrawals due to death (Table 27)

In this Table, for each of the 9 patients that died (UDCA=3; PL=6), clinical/biochemical data at randomization (at entry) and the reason for death are given.

b) Withdrawals due to liver transplantation or referral for liver transplantation (Table 28)

In addition to listing the individual patients per group and date of randomization, this table briefly summarizes the more recent developments preceding the referral for transplantation (OLT).

TABLE 27  
Mayo Clinic Trial

Withdrawals Due to Deaths

UDCA [n=3]			PLACEBO [n=6]		
Pt. ID# Age, Sex	Date of Randomization/ Findings at BL	Date of Withdrawal/ Reason for Death	Pt. ID# Age, Sex	Date of Randomization/ Findings at BL	Date of Withdrawal/ Reason for Death
#746 59y F	10/27/88: Moderate pruritus, mild fatigue, with portal hypertension, ascites + varices, BIL=1.5, AP=1617, OT=102, ALB=3.4, Histologic stage=7. On diuretics.	10/23/90: Ruptured splenic varix hilum bleed*	#708 64y M	5/25/88: Jaundiced (BIL=5.1), hepatomegaly, Xanthelasma, moderate pruritus and moderate fatigue, varices (neither ascites nor PSE), AP=3052, OT=139, ALB=2.6, Histologic Stage=IV. On steroids.	7/22/90: End stage PBC*
#804 69y F	8/11/89: Moderate pruritus, mild fatigue, hepato-splenomegaly, edema, osteoporosis, osteodystrophy, esophageal varices, AP=2062, BIL=2.8, OT=95, ALB=2.5, Histologic Stage=IV (Fibrosis grade 3). On Questran, steroids (for PBC).	W/D date 6/4/90; Death date 11/16/90: End stage PBC*	#752 58y F	11/17/88: Xanthelasma, mild pruritus, mild fatigue, BIL=0.6, AP=1262, OT=80, ALB=3.1, Histologic Stage=III.	11.3.89: Pulmonary Blastomycosis pneumonia*
#819 69y F	11/22/89: Jaundiced, mild pruritus, moderate fatigue, with esophageal varices, xanthoma, hepatomegaly, osteoporosis, osteodystrophy, thyroid Hashimoto, AP=1630, BIL=1.1, OT=107, ALB=2.8, no data on histologic stage. Had been on colchicine, Questran.	6/4/91: End stage PBC*	#763 61y F	12/8/88: Sicca syndrome, osteoporosis, mild fatigue, BIL=1.1, AP=627, OT=67, ALB=3.4, Histologic Stage=IV. Had been on steroids, Questran, D-PEN, diuretics	1/24/89: Esophageal varixal bleed*

TABLE 27 (Con't)

	#784 65y F	6/1/89: Hx of portal shunt, sicca syndrome, jaundiced (BIL=11.2), hepatomegaly, hematemesis, edema, osteoporosis, moderate pruritus, severe fatigue, AP=1570, OT=210, ALB=2.5, histologic stage=IV with grade 3 fibrosis. On diuretics.	2/28/90: End stage PBC
	#802 52y F	8/1/89: Moderate pruritus, mild fatigue, portal hypertension, BIL=1.0, AP=1358, OT=73, ALB=3.0. Histologic stage=III. On steroids for indication other than PBC.	11/6/90: Head trauma - automobile accident
	#844 65y M	7/12/90: Moderate pruritus, mild fatigue, associated Sjögren's syndrome and Raynaud's syndrome, BIL=1.2, AP=2064, OT=174, ALB=3.8.	7/31/91: Metastatic esophageal cancer

a) This produced exsanguination. Pt. autopsy: portal hypertension and hyperplenism.  
b) W/D from the trial for financial reasons.  
c) Pt.'s daughter informed site that pt. had died secondary to end stage PBC.  
d) By report from his local medical doctor; no further information available.  
e) By report from her local medical doctor; no further information available.  
f) Intractable esophageal varix bleed; ventilator assistance removed.  
g) Developed hepatic encephalopathy and coma. Febrile at the end.

TABLE 28  
Mayo Clinic Trial

Withdrawals Due to Liver Transplant or  
Referral for Liver Transplant

UDCA [n=3]			PLACEBO [n=5]		
Pt. ID# Age, Sex	Date of Randomization	Date of Withdrawal/ Reason for Withdrawal	Pt. ID# Age, Sex	Date of Randomization	Date of Withdrawal/ Reason for Withdrawal
#728 53y F	7/28/88	4/22/90: Transplant. She experienced recurrent variceal bleeds, ascites and developed spontaneous bacterial peritonitis which was secondary to an acute appendicitis with perforation. Her post-surgical course included significant deterioration in her liver and renal function and she was placed on hemo-dialysis. She then experienced repeated upper GI bleeding secondary to candida esophagitis and/or a GU. A combined OLT followed by a renal transplantation was performed on 4/22/90.	#756 63y F	11/16/88	1/16/89: Referred for transplant. Had long Hx of PBC. Developed worsening of lower extremity edema and bleeding esophageal varices.
#757 52y F	11/29/88	1/10/90: Viral hepatitis/transplant. This patient was evaluated in 1/90 for increasing jaundice, hypertransaminemia and hyperbilirubinemia. Her study medication was stopped at this time. The patient was evaluated in 3/90 for progression of her PBC with atypical features of PBC consisting of hypertransaminemia. It was felt that this was most likely the result of intercurrent hepatitis. Due to this and her declining clinical condition she underwent liver biopsy which demonstrated features of PBC and severe unresolved cholestatic lobular viral hepatitis. By verbal report from the Mayo Clinic Rochester Study Coordinator she later underwent OLT.	#765 42y F	12/1/88	3/13/90: End-stage PBC - referred for transplant. Experienced a recent rise in her total BIL to 13 mg/dl over the past 2 years. Test med. was stopped the previous month without improvement.

TABLE 28 (Con't)

<p>#852 49Y F</p>	<p>8/24/90</p>	<p>1/15/91: Referred for transplant. She elected to stop test med. in 1/91 and was placed on the transplant list in [REDACTED]. Leg and stomach cramping stopped when she D/C test med.</p>	<p>#774 50Y F</p>	<p>3/7/89</p>	<p>3/15/91: End-stage PBC - referred for transplant.</p>
			<p>#808 56Y F</p>	<p>9/21/89</p>	<p>3/12/91: Referred for transplant. Her PBC had progressed based on the information of diuretic-controlled fluid retention and lowering of her serum ALB. Based on her current laboratory findings and the Mayo Cox Model, her risk of dying without transplantation was greater than that with transplantation.</p>
			<p>#832 43Y F</p>	<p>3/7/90</p>	<p>10/1/91: End-stage PBC - referred for transplant by her physician in Scottsdale, AZ.</p>

c) Withdrawals due to other reasons

The following two patients (UDCA=1, PL=1) withdrew from the trial to enter other studies or for reasons of non-compliance.

## Withdrawals Due to Other Reasons

Pt. ID# Age, Sex	Treatment Group	Date Randomized Into Trial	Date Withdrew From Trial	Reason for Withdrawal
799 48y M	PL (n=1)	7/13/89	9/5/91	Entered UDCA/MTX study. Developed esophageal varices, which would put him in the category of Tx Fx for the trial.
753 51y F	UDCA (n=1)	11/17/88	6/6/91	Non-compliance

d) Voluntary withdrawals (Table 29)

In this Table, the reasons for voluntary withdrawals in 15 patients (UDCA=4; PL=11) are summarized.

- Of the 11 PL patients, 4 W/D for financial reasons, 4 were non-compliant (2 of these never took test medication, one was unwilling to return for F/U visits and the other did not wish to continue in the trial). Two of the remaining 3 patients elected to W/D from the trial (no details given) and the other asked her physician to be decoded and W/D from the trial. She entered the UDCA/MTX trial.
- The 5 UDCA-treated patients that W/D voluntarily did not appear to be responding well to test medication. One felt she was unable to tolerate the drug even at lower doses due to pruritus, another chose to be managed locally for variceal bleeding. In the 3rd and 4th patients the clinical/biochemical condition was deteriorating (in one of these BIL levels were rising, in the other varices had developed, BIL levels were high and there were histological signs of disease progression). The fifth patient stated she experienced nausea and vaginal bleeding while on the drug.

TABLE 29  
Mayo Clinic Trial  
Voluntary Withdrawals

UDCA [n=4]			PLACEBO [n=11]		
Pt. ID # Age, Sex	Date of Randomization	Date of Withdrawal/ Details of Withdrawal	Pt. ID # Age, Sex	Date of Randomization	Date of Withdrawal/ Details of Withdrawal
704 49Y F	4/27/88	Voluntary. [Due to dissatisfaction with her scheduled Tx visit plus the fact that she felt she was unable to tolerate the drug even at lower dose due to pruritus].	718 46Y F	6/29/88	8/1/90: Voluntary withdrawal.
706 69Y F	5/18/88	Voluntary. [She chose to be managed locally for variceal bleeding]	743 42Y F	10/19/88	5/1/90: Financial reasons.
770 66Y F	1/5/89	Voluntary. Physician's advice. [Her clinical condition was deteriorating and her BIL levels were rising. On this basis the blind was broken, test med. was stopped for this patient and she W/D].	766 35Y F	12/5/88	6/15/90: Financial reasons.

TABLE 29 (Con't)

816 46Y F	10/16/89	9/27/91: Voluntary. [Reevaluated in 9/91 when it was found that her disease had progressed clinically, biochemically and histologically. She was considered a Tx Fx due to the development of varices and an increase in her BIL levels. The pt. elected to remove herself from this trial so that she could be considered for the UDCA/MTX trial.]	769 43Y F	1/5/89	7/1/91: Voluntary withdrawal. (Clinically stable in 2-year visit of 5/29/91).  (Entered UDCA/MTX trial).
851 41Y F	3/20/90	5/15/91: Voluntary - Due to symptoms. [She stated she experienced nausea and vaginal bleeding while on the drug.]	772 42Y F	1/17/89	9/26/89: Non-compliant. [Never took test med.]
			773 43Y F	2/13/89	8/15/89: Non-compliant. [Never took test med.]
			814 54Y F	10/13/89	7/15/90: Voluntary withdrawal.
			817 28Y F	11/6/89	11/15/91: Financial reasons.
			822 55Y F	12/18/89	1/22/90: Financial reasons.
			826 59Y F	1/18/90	6/15/91: Non-compliant. [Unwilling to return for F/U visits]
			853 49Y F	6/27/90	2/15/91: Non-compliant. [Did not wish to continue in the trial]

3) Patients dechallenged and rechallenged  
(Table 30)

A total of 7 patients (UDCA=3; PL=4) underwent dechallenge and/or rechallenge for reasons summarized in Table 30. Generalizations are not possible due to the small number of patients involved. With UDCA, pruritus was a problem in two patients. In one of these, pruritus disappeared when the drug, which had been stopped for one week, was gradually introduced. In the other pt. the drug appeared to be associated with increased itching. This was not yet controlled by the one year evaluation, even though the dose was decreased to one tablet per day. The pt. withdrew voluntarily.

It is of interest to note that there were no cases of diarrhea among the patients taking UDCA.

TABLE 30  
 Mayo Clinic Trial

Dechallenge/Rechallenge Data

Reason for Dechallenge	UDCA (n=3)	PL (n=4)
PRURITUS	<p><u>Pt. #701</u>                      This 51y F stopped test med. for one week due to the development of pruritus. The drug was then restarted at a dose of one tb. per day for one week, ↑ by one day each week until desired dose was reached. The pt. had no further difficulty with pruritus.</p> <p><u>Pt. #704</u>                      This 49y F had to resume Questran after starting test med. due to ↑ itching. After the 1 year evaluation she tried a ↓ dose of one tablet per day, but was unable to tolerate it. Her pruritus continued. After 9 days, she W/D voluntarily (see Table 29).</p>	0
DIARRHEA	0	<p><u>Pt. #708</u>                      [64y M]. After one month of test med. this dose was reduced to 2 tbs. per day due to diarrhea. He remained on this regimen as the patient was unable to take &gt;2 tbs. per day, as the diarrhea continued to be a problem.</p>

INCREASED BILIRUBIN	0	<p><u>Pt. #718</u>  This 46y F patient entered the trial with a serum BIL level of 1.2; &gt;7 mo. later the test med was stopped after total serum BIL had ↑ to 6. One mo. later the value was 3.7. Test med. was resumed at a gradual dose. Serum BIL remained stable and eventually went down. Ca. 2y after randomization into the trial, the pt. was D/C and the CTM stopped.</p>
RED SPOTS ON TONGUE	0	<p><u>Pt. #719</u>  2 mo. after the beginning of the trial, the development of red spots on the tongue of this 58y F prompted a reduction in dose of CTM from 4 tbs. per day to 2 per day. The dose was then gradually ↑ to 4 per day when the symptoms cleared.</p>
FEVER + GI SYMPTOMS	0	<p><u>Pt. #729</u>  Ca. 2.5 mo. after entering the trial, test med. was stopped in this 54y F patient because of lower Abd. pain, fever, N&amp;V and diarrhea. Two weeks later she resumed taking one tb. per day, but similar symptoms recurred the subsequent week. After 2 additional weeks the drug was resumed at a dose of 1 tb. per day and gradually increased to the full dose with no problems.</p>
	0	<p><u>Pt. #744</u>  In this 50y F patient, the test med. was stopped ca. 3 weeks after the start due to abd. discomfort, probably representing post-liver Bx pain, which gradually subsided. Test med. was resumed gradually starting 10 days after D/C.</p>

#### 4) Changes in vital sign parameters

At baseline, the two treatment groups were similar to each other in mean systolic and diastolic blood pressure and body weight. At endpoint, there was a statistically significant decrease from baseline ( $p < 0.05$ ) in mean systolic blood pressure (change from BL, UDCA = -4.19 mmHg, PL = 1.14 mmHg) and a significant increase ( $p < 0.05$ ) in mean weight (change from BL, UDCA = 1.35 Kg, PL = 0.38 Kg) for the UDCA-treated group. The mean values were associated with extremely large SDs. These changes are mentioned here for completeness but they do not seem to be of concern. The sponsor states that distribution of physical exam by visit 12 and 24 indicated that the majority of patients did not have any significant change from BL in physical exam findings at 12 or 24 month visits (sponsor's Tables BF and BG; Tables Following Text). Also

comparable between the two treatment groups was the distribution of change in symptoms from BL to 12 or 24 months (sponsor's Tables BH and BI; Tables Following Text).

5) Changes in laboratory parameters

- The change in urinalysis parameters to endpoint from BL was not statistically different between the two treatment groups.
- Changes in non-hepatic clinical chemistries from baseline were summarized in sponsor's Table 36 (vol. 35, p. 080). At baseline the two groups were similar to each other in all of these parameters which included Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>++</sup>, Phosphorus, glucose, creatinine, CHOL, TG, HDL, total thyroxine and AMA<sub>s</sub>. There were some quantitative changes, some minor, to endpoint from BL, for some of these parameters. Statistically significantly different from zero were the changes in Ca<sup>++</sup>, creatinine and CHOL for PL-treated patients. Once again, these changes were associated with very large SDs and a lot of overlapping. Only the changes for two parameters, CHOL and AMA<sub>s</sub>, are commented further upon. For all other parameters, UDCA could not be differentiated from PL.
- The changes in CHOL are summarized as follows:

Serum Cholesterol (mg/dl)\*: Changes from Baseline

Baseline		Endpoint		Change from BL		p-value UDCA vs PL
UDCA (n=89)	PL (n=91)	UDCA (n=83)	PL (n=76)	UDCA	PL	
287.73 <sup>b</sup> (121.12)	276.03 (105.22)	223.53 (56.80)	261.46 (83.53)	-67.39 <sup>**</sup> (93.31)	-11.32 <sup>*</sup> (47.70)	0.0001

a) Depicted are the mean and  $\pm$ SD of the mean.  
 b) UDCA vs PL at Baseline, p=N.S.  
 \* Statistically different from zero, p<0.05  
 \*\* Statistically different from zero, p<0.01

- The changes in AMA<sub>s</sub>, as presented by the sponsor, are summarized below.

AMA<sub>s</sub> : Changes from BL\*

Baseline <sup>b</sup>		Endpoint <sup>c</sup>		Change from BL		p-value UDCA vs PL
UDCA (n=87)	PL (n=91)	UDCA (n=6)	PL (n=5)	UDCA	PL	
2810.57 (4892.34)	3206.59 (6496.17)	166.67 (263.11)	2048.00 (1941.22)	-713.33 (794.47)	-6176.0 (8129.83)	N.S. <sup>d</sup>

a) Depicted are the mean  $\pm$ SD of the Mean.  
 b) At baseline, there was no significant difference between the two treatment groups.  
 c) The number of observations at endpoint is very small, in comparison to observations at baseline.  
 d) Difference in change in AMA<sub>s</sub> between the two treatment groups was not statistically significant.

- Hb did not change significantly. In the UDCA-treated group there was a significant decrease in WBC and platelets from baseline (both at  $p < 0.01$ ). In the PL-treated group, there was a significant ( $p < 0.05$ ) decrease in platelets from baseline. All these changes were associated with large SDs, were not statistically different between the treatment groups and did not seem clinically important.

#### 6) Effects on bone mineral density

As shown below, the two treatment groups did not differ at baseline in BMD or in BMD%. There was a significant ( $p < 0.01$ ) decrease in BMD (but not BMD%) to endpoint from BL in the UDCA-treated group. Difference in change in BMD (or BMD%) between the two treatment groups was not statistically significant.

Bone Mineral Density: Change at Endpoint from Baseline

	Baseline*		Endpoint*		Change from Baseline		
	UDCA	PL	UDCA	PL	UDCA ( $\pm$ SD)	PL ( $\pm$ SD)	p-value UDCA vs PL
BMD	[n=71] 1.01 (0.21)	[n=68] 1.05 (0.22)	[n=78] 0.92 (0.20)	[n=63] 1.00 (0.21)	-0.09** (0.17)	-0.06 (0.23)	N.S.
BMD %	[n=69] 45.7 (26.2)	[n=65] 52.4 (29.0)	[n=77] 48.2 (31.6)	[n=63] 51.5 (31.9)	-0.2 (22.8)	-0.38 (16.9)	N.S.

a,b) Depicted are the mean  $\pm$ SD of the Mean.

\*\* Statistically different from zero,  $p < 0.01$

#### 7) Effects on chest X-ray and endoscopy findings

There was no statistically significant change at endpoint from baseline in chest x-ray or endoscopy data.

#### 9. Sponsor's Conclusions

"The results of this trial indicate the following:

- "UDCA at a dosage of 13 to 15 mg/kg per day for two years is more effective than placebo in delaying the progression of the disease (as measured by the time to treatment failure) and inducing improvement in biochemical markers in patients with primary biliary cirrhosis.
- "UDCA at the 13 to 15 mg/kg per day dosage appears to be generally well-tolerated and has no clinically significant adverse effects.
- "Results provide unequivocal demonstration of the premises set forth in the study protocol."