C. Mayo Clinic Study Double-Blind Phase

C.1 Study Protocol and Outcome Measures

The multicenter, randomized, double-blind placebo-controlled study was conducted to evaluate the safety and efficacy of ursodeoxycholic acid given at a dose of 13-15 mg/kg/day (administered in 4 individual doses as UDCA tablet, say 250mg) in patients with primary biliary cirrhosis (PBC). The study was designed so that the blind would be maintained until all patients had completed 2 year of doubled-blind treatment at which time all patients were offered an option to participate in the open-label UDCA treatment, long-term follow-up extension.

The sample size required to detect a 25% reduction in proportion of patient failing in the UDCA group (assuming a failing rate of about 60 % in the placebo control group), with a 80 percent power and 5 percent significance level was determined by sponsor to be 114 patients randomized (57 in each of the two treatment groups). Controlling for an estimated dropout rate of 7%, a minimum of 132 patients was to be enrolled. One hundred and eighty patients were actually randomized in this trial.

One hundred and eighty patients with PBC were recruited in four centers and randomized into the study. Patients were stratified into eight strata according to histologic stage (I and II vs. III and IV), serum bilirubin level ($\leq$ 1.8 mg/dL vs. > 1.8 mg/dL) and esophageal varices (present vs. absent). In total, there were 112 patients that completed at least two years of treatment. The maximum length of treatment in double-blinded stage was four years. For the purpose of the analysis of double-blind trial, only the experience in the first two years was used.

The primary outcome is the incidence of and time to treatment failure during the first 2 years of double-blind treatment. The treatment failure is defined as:

1) Death
2) Need for liver transplantation
3) Histological progression by two stages or to cirrhosis
4) Development of varices, ascites, encephalopathy
5) Doubling of bilirubin (second measurement >1.5 mg/dL)
6) Marked worsening of fatigue or pruritus
7) Inability to tolerate the drug
8) Voluntary withdrawal

The secondary outcomes are:

1) Change in alkaline phosphate (ALP), AST(SGOT), bilirubin, albumin, IgM and prothrombin time (PT)
2) Change in symptoms such as fatigue or pruritus

3) Development of clinical progression of esophageal varices, ascites or edema and encephalopathy
4) Histological change

C.2 Sponsor's Analysis

There were 180 patients randomized into the trial, 86 patients each received the placebo or UDCA treatment. All data are truncated at 2 years in the efficacy analyses. The flow chart of the patients in the trial is given in the following table

Table 2 Patient Flow Chart/Mayo Study Double Blind Phase

SUBGROUP	PLACEBO	UDCA
Randomized	91	89
Completed baseline only	5	3
Total received any treatment	86	86
Received more than 2-years of treatment	49	63
Received less than 2-year treatment	27	20
Treatment success at last visit	46	66
Treatment failure at last visit	40	20
Discontinuation due to treatment failure	22	11
Death	6	3
Voluntary withdrawal	11	5
Transplant	5	3
Failure due to Double of bilirubin Varices/ascites/PSE Histological progression Worsening of symptoms	18	9
Other reasons	1	1

C.2.1 Treatment Group Comparability

Although this trial enrolled patients in four centers (Rochester, Jacksonville, Scottsdale and Scott & White), 160 of the 180 patients (and 144 of 152 patients receiving any treatment) were enrolled at Rochester center. Because one of the centers consists of more than 95% of the patients, data are analyzed with all centers combined.

The comparability of treatment groups at baseline is summarized in Tables A1- A6 (in

Appendix). There are no obvious differences in the baseline data. The differences between the two treatment groups are not statistically significant in demographic measurements, symptoms of pruritus and fatigue and duration of diagnosis, etiological factors, surgical history at baseline or pharmacologic treatment received within 3 months prior to baseline.

C.2.2 Analyses of Primary Outcomes

The primary efficacy outcome is the treatment failure which consists of drug toxicity, death, voluntary withdrawal, liver transplantation, doubling of total bilirubin, marked worsening of fatigue or pruritus, development of varices, ascites or encephalopathy, histological progression by two stages or to cirrhosis. The comparisons are made in percentage of failures and in time to failures.

C.2.2.1 Comparisons of Percentage of Treatment Failures

The comparisons are summarized in Table 3. Patients in the UDCA group had significantly lower percentage of all failures than the placebo group (23% vs. 47%, $p<0.01$) and of doubling of total bilirubin (2% vs. 13%, $p=0.01$). Numerically, the UDCA group has lower percentage than placebo group in almost every failure category, indicating consistency across failure categories (See also TableA7 in Appendix).

Table 3 Summary of Treatment Failures/Mayo Study Double Blind Phase

STUDY OUTCOME	PLACEBO n(%)	UDCA n(%)	UDCA - PLACEBO(%) (P-VALUE[1])
Patients Received Treatment	86	86	
All Failures	40(47)	20(23)	-24 (<0.01)
Doubling of Total Bilirubin	11(13)	2(2)	-9(0.01)

1: Fisher's Exact Test

C.2.2.2 Comparisons of time to failure

Life table analysis for the comparison of time to failure is carried out for the primary outcome (all failures combined). The comparisons are also made with stratification by total bilirubin and histologic stage at baseline. The comparisons on time to all failure are summarized in the following table and Figure A. The mean time to treatment failure are compared using both the log rank test and the Wilcoxon test. In the log rank test, each failure is treated with equal weight in the test, while in the Wilcoxon test, more weight is given to earlier failure by weighting proportionally to the number exposed at

the time. Hence Wilcoxon test is more sensitive to the earlier failures than the log rank test. The log rank test is also more powerful when the ratio of hazard rates of the UDCA and the placebo groups is a constant (i.e. constant hazard or propostional hazard). The Wilcoxon test is more powerful when the ratio of hazard rates is not constant. Both of the tests may be biased when the censoring is not random or unequal between the two treatment groups (Elisa T. Lee, Statistical Methods for Survival Data Analysis, 2nd edition, John Wiley and Sons, Inc., New York, 1992).

Patients in the placebo group has significantly shorter mean time to failure than those in the UDCA group in all patients analysis and in each of the strata using the log rank test. The difference is not statistically significant in patients with baseline total bilirubin greater than 1.8 mg/dL when the Wilcoxon test was used (p=0.06). The Cox proportional hazard model and logistic regression are performed with baseline total bilirubin and histologic stage as covariate in the model. Treatment failure is statistically higher (p<0.001) in the placebo group.

Table 4 Summary of Time to Failure (in Days) Comparison/Mayo Study Double Blind Phase

BASELINE STRATIFICATION		TIME TO TREATMENT FAILURE		
		PLACEBO	UDCA	UDCA-PLACEBO (P-VALUE[1])
All Patients	n	86	86	
	Mean	641.1	803.8	162.7(0.0001)
	std	24.3	24.9	
	Number failed	40	20	
Total Bilirubin ≤ 1.8mg/dL	n	63	65	
	Mean	656.0	821.6	165.6(0.003)
	std	29.3	27.1	
	Number Failed	24	14	
Total Bilirubin > 1.8 mg/dL	n	23	21	
	Mean	612.7	737.1	124.4(0.01)
	std	46.4	42.5	
	Number Failed	16	6	

BASELINE STRATIFICATION		TIME TO TREATMENT FAILURE		
		PLACEBO	UDCA	UDCA -PLACEBO (P-VALUE[1])
Histologic Stage I & II	n	23	29	
	Mean	675.7	755.5	77.8(0.02)
	std	42.9	3.3	
	Number Failed	9	4	
Histologic Stage III & IV	n	59	54	
	Mean	624.7	805.2	180.5(0.0003)
	std	30.6	32.0	
	Number Failed	29	13	

1: log rank test.

C.2.2.3 Comparisons of time to death or liver transplant

Life table analysis for the comparison of time to death or liver transplantation is performed with all patients. The comparisons are also made with stratification by total bilirubin and histologic stage at baseline. The comparisons of time to death or liver transplant are summarized in the following table and Figures B-D. The mean time to death or liver transplant are compared using both the log rank test and the Wilcoxon test. There are no statistical differences between the placebo and the UDCA group in all patients analysis and in each of the strata using either the log rank test or the Wilcoxon test. The conclusion does not change when the baseline total bilirubin and histologic stage are entered as covariates in the Cox proportional hazard model or logistic regression analysis.

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Table 5 Summary of Time to Death or Liver Transplantation (in Days) Comparison/ Mayo Study Double Blind Phase

BASELINE STRATIFICATION		TIME TO DEATH/TRANSPLANT		
		PLACEBO	UDCA	UDCA - PLACEBO (P-VALUE[1])
All Patients	n	86	86	
	Mean	732.1	707.0	-25.1[a](0.11)
	std	18.5	10.1	
	Number failed	11	6	
Total Bilirubin ≤ 1.8mg/dL	n	63	65	
	Mean	451.8	707.5	255.7[a](0.85)
	std	8.1	12.8	
	Number Failed	4	4	
Total Bilirubin > 1.8 mg/dL	n	23	21	
	Mean	681.9	623.5	-58.9[a](0.06)
	std	45.2	13.1	
	Number Failed	7	2	
Histologic Stage I & II	n	23	29	
	Mean	462.9	No estimate	n/a
	std	5.7	No estimate	
	Number Failed	2	0	
Histologic Stage III & IV	n	59	54	
	Mean	728.7	615.2	-113.5[a](0.14)
	std	24.3	12.4	
	Number Failed	8	4	

1: log rank test
a: Estimation may be biased toward the placebo group due to heavier censoring in the placebo group and at the end of the study

An additional analysis using Cox proportional hazard model with Mayo risk score at baseline entering as covariate reduces the p-value of the difference to 0.07.

Table 6 Time to Death or Liver Transplantation Adjusted for Baseline Mayo Risk Score/Mayo Study Double Blind Phase

	P-VALUE
Treatment Group Comparison	0.07[a]
Mayo Risk Score	0.0001[a]
Treatment by Mayo Risk Score Interaction	0.27[a]

a: Cox proportional hazard model: testing for ratio of hazard rates =1.

C.2.3 Analyses of secondary outcomes

C.2.3.1 Comparisons of Hepatic biochemical markers

Hepatic biochemical markers, including alkaline phosphatase, SGOT, total bilirubin, prothrombin time, Albumin, IgM, IgA, IgG and gamma globulin, are compared between the two groups in terms of changes at the end of the trial from baseline. The comparisons are summarized in Table 7. There are significant decreases from baseline in total bilirubin, IgM, IgG, in the UDCA-treated patients. In placebo group, there are significant increases in SGOT, total bilirubin, PT, IgA and gamma globulin. When comparing the changes from baseline, In all markers except albumin, the differences are significant in favor of the UDCA-treated group.

Table 7 Hepatic biochemical markers: change from baseline/Mayo Study Double Blind Phase

HEPATIC BIOCHEMICAL MARKER		BASELINE		END OF TRIAL		CHANGE FROM BASELINE		
		Placebo	UDCA	Placebo	UDCA	Placebo (std)	UDCA (std)	UDCA-Placebo(se)
Alkaline Phosphatase (IU/L)	Mean (std)	1256.09 (710.55	1334.09 (931.43)	1259.78 (738.15)	622.52 (422.8)	14.67 (562.63)	-708.38** (690.79)	-723.38[b] (99.07)
	n	91	89	76	83	76	83	
SGOT (IU/L)	Mean (std)	97.49 (48.17)	99.35 (45.86)	120.38 (66.76)	63.88 (40.47)	25.51** (57.23)	-36.20** (40.44)	-61.7 [b] (7.83)
	n	91	89	76	83	78	83	
Total Bilirubin mg/dL	Mean (std)	1.76 (2.26)	1.86 (2.33	2.29 (2.53)	1.27 (1.39)	0.80** (1.86)	-0.63** (1.80)	-1.48[b] (0.29)
	n	91	89	76	83	78	83	

HEPATIC BIOCHEMICAL MARKER		BASELINE		END OF TRIAL		CHANGE FROM BASELINE		
		Placebo	UDCA	Placebo	UDCA	Placebo (std)	UDCA (std)	UDCA - Placebo (se)
Prothrombin Time (PT)	Mean (std)	11.63 (0.83)	11.75 (1.28)	11.91 (0.83)	11.70 (0.81)	0.26* (0.85)	-0.05 (1.08)	-0.37[c] (0.15)
	n	90	87	73	83	73	83	
Albumin	Mean (std)	3.33 (0.41)	3.40 (0.44)	3.36 (0.43)	3.52 (0.44)	0.03 (0.49)	0.12* (0.49)	0.09[a] (0.077)
	n	91	89	76	83	78	83	
IgM	Mean (std)	491.57 (314.99)	675.91 (423.16)	512.06 (377.13)	520.30 (337.34)	31.78 (219.29)	-151.89** (292.04)	-783.67[b] (40.85)
	n	82	82	75	83	75	83	
IgA	Mean (std)	297.57 (134.71)	272.16 (118.44)	317.39 (148.73)	267.61 (134.29)	26.17** (60.81)	-1.11 (83.77)	-27.28[c] (11.57)
	n	82	82	75	83	75	83	
IgG	Mean (std)	1710.11 (482.82)	1619.83 (581.32)	1735.95 (524.39)	1526.78 (533.72)	59.55 (336.67)	-93.96* (362.10)	-153.51[c] (55.60)
	n	82	82	75	83	75	83	
Gamma Globulin	Mean (std)	1.88 (0.51)	1.93 (0.57)	2.04 (0.56)	1.87 (0.64)	0.14** (0.41)	-0.03 (0.58)	-0.17[c] (0.079)
	n	90	87	75	83			

*: $p < 0.05$, paired t-test for H_0: μ(change from baseline) =0
**: $p < 0.01$, paired t-test for H_0: μ(change from baseline) =0
a: $p > 0.05$, t-test for H_0: μ(change from baseline in UDCA) =μ(change from baseline in Placebo)
b. $p < 0.0001$, t-test for H_0: μ(change from baseline in UDCA) =μ(change from baseline in Placebo)
c: $p < 0.05$, t-test for H_0: μ(change from baseline in UDCA) =μ(change from baseline in Placebo)

C.2.3.2 Comparisons of status of cirrhosis, ascites,varices and portal systemic encephalopathy

The comparisons of the percentage of incidence are summarized in Table 8. There are no significant differences between the UDCA and the placebo groups in the incidence of cirrhosis, ascites, varices or portal systemic encephalopathy.

Table 8 Summary of Percent of Cirrhosis, Ascites, Varices and Portal Systemic Encephalopathy/Mayo Study Double Blind Phase

SYMPTOM		PLACEBO	UDCA	UDCA-PLACEBO (P-VALUE[1])
Status Interval (Days from Entry to Yes Status)	Mean (std)	580 (215)	654 (171)	74(0.01)
	n	86	86	
Cirrhosis	n(%)	30 (49)	22(33)	-16[2](0.07)
Varices	n(%)	28(45)	23(34)	-11(0.28)
Ascites	n(%)	5(7)	4(5)	-2(0.74)
PSE	n(%)	1(1)	0(0)	-1(0.47)
Discontinued From Study n(%)		23(27)	12(14)	-13(0.06)

1: t-test for status interval H_0: $\mu_{UDCA} = \mu_{placebo}$, exact for others H_0: $P_{UDCA} = P_{placebo}$.
2: difference in percentage.

C.2.3.3 Changes in pruritus and fatigue from baseline

Treatment difference in changes from abseline are not significant.

Table 9 Summary of Changes in Pruritus and Fatigue from Baseline/Mayo Study Double Blind Phase

SYMPTOM	MEAN (SD)	BASELINE		ENDPOINT		CHANGE		DIFF
		PLACEBO	UDCA	PLACEBO	UDCA	PLACEBO	UDCA	
Pruritus	Mean (std)	0.8 (0.9)	0.8 (0.8)	0.9 (0.8)	0.6 (0.7)	**0.01 (0.8)**	-0.2 (0.8)	-0.21 P=0.18[a]
	n	91	89	76	83	76	83	
Fatigue	Mean (std)	0.9 (0.8)	1.0 (0.8)	0.9 (0.8)	0.7 (0.8)	-0.03 (1.0)	-0.2 (0.9)	-0.18 P=0.19
	n	91	89	76	83	76	83	

a: t-test for H_0: μ(change from baseline in UDCA) =μ(change from baseline in Placebo)

C.2.3.4 Changes from baseline in biliary bile acids

The comparisons of changes from baseline in biliary bile acids are summarized in Table 10. There are significant changes in ursodeoxycholic, cholic, chenodeoxycholic and lithocholic acids in the UDCA group. The changes are also significant in ursodeoxycholic and chenodeoxycholic acids in the placebo group. However, the increases in ursodeoxycholic and lithocholic acids are significantly greater in the UDCA

group than the placebo group, but the decreases in cholic and chenodeoxycholic acids are significantly greater in the UDCA group than in the placebo group.

Table 10 Biliary Bile Acids: Change from Baseline/Mayo Study Double Blind Phase

PARAMETER		BASELINE		VISIT AT 24 MONTH		CHANGE FROM BASELINE		
		Placebo	UDCA	Placebo	UDCA	Placebo (std)	UDCA (std)	UDCA-Placebo(se)
Ursodeoxycholic	Mean (std)	1.39 (1.37)	1.39 (1.21)	13.07 (23.39)	43.92 (20.25)	8.13** (19.54)	42.28** (20.44)	34.15[a] (3.69)
	n	80	78	57	61	57	61	
Cholic	Mean (std)	54.17 (17.53)	54.15 (18.16)	47.15 (23.14)	27.53 (18.40)	-1.37 (20.96)	-25.14** (19.87)	-23.77[a] (3.76)
	n	79	78	57	61	57	61	
Chenodeoxy-cholic	Mean (std)	33.52 (12.09)	32.16 (12.13)	28.43 (13.42)	18.39 (7.51)	-6.74** (12.66)	-13.20** (11.85)	-6.46[b] (2.26)
	n	79	78	57	61	57	61	
Deoxycholic	Mean (std)	10.23 (11.16)	10.36 (13.31)	9.88 (13.03)	9.84 (11.69)	-0.26 (14.38)	-1.62 (15.21)	-1.37[c] (2.73)
	n	77	78	57	81	57	61	
Lithocholic	Mean (std)	0.35 (0.76)	0.18 (0.35)	0.36 (0.70)	0.80 (1.25)	-0.05 (1.11)	0.51** (1.06)	0.56[b] (0.20)
	n	77	78	58	60	58	61	
Sulfa-lithocholic Acid-lithocholic	Mean (std)	0.29 (0.45)	0.36 (0.86)	0.63 (2.11)	0.42 (0.83)	0.15 (1.26)	0.03 (0.89)	-0.12[c] (0.20)
	n	77	78	58	61	75	61	

**: $p < 0.01$ paired t-test for H_0: μ(change from baseline) =0

a : $p < 0.001$ t-test for H_0: μ_{UDCA}(change from baseline) = $\mu_{placebo}$(change from baseline)

b : $p < 0.01$ t-test for H_0: μ_{UDCA}(change from baseline) = $\mu_{placebo}$(change from baseline)

c : not significant t-test for H_0: μ_{UDCA}(change from baseline) = $\mu_{placebo}$(change from baseline)

C.2.3.5 Stages of histologic at endpoint

There is no significant difference in the percentage of patients in stages of disease at either baseline or endpoint. The comparisons are summarized in Table 11.

Table 11 Changes of Histologic Stage from Baseline/Mayo Study Double Blind Phase

STAGE OF DISEASE	BASELINE			ENDPOINT		
	PLACEBO n(%)	UDCA n(%)	P-VALUE*	PLACEBO n(%)	UDCA n(%)	P-VALUE*
I	3(3)	7(8)	0.57	4(11)	1(2)	0.77
II	22(25)	23(27)		9(16)	7(16)	
III	36(41)	31(36)		28(49)	22(51)	
IV	26(30)	25(29)		16(28)	13(30)	

*: Chi-squared test for H_0: P_{UDCA} (stage I) = $P_{placebo}$(stage I)

C.2.3.6 Mayo risk score

The comparisons between the two treatment group are summarized in Table 12. The Mayo risk score increases from baseline to the endpoint significantly in the placebo group but decreases significantly instead in the UDCA group. The changes are significant different (UDCA-placebo=-0.6, p<0.001 based on t-test)

Table 12 Changes of Mayo Risk Score from Baseline/Mayo Study Double Blind Phase

MAYO RISK SCORE	BASELINE		ENDPOINT		CHANGE FROM BASELINE		
	Placebo	UDCA	Placebo	UDCA	Placebo	UDCA	UDCA-Placebo
Mean	5.0	5.1[a]	5.3	4.8	0.3*	-0.3*	-0.6**
std	1.1	1.1	1.1	1.1	0.7	0.6	
n	90	87	73	83	72	82	

a : not significant for t-test for H_0: μ_{UDCA}(baseline) = $\mu_{placebo}$(baseline)
*: p < 0.01 paired t-test for H_0: μ(change from baseline) = 0
**: p < 0.001 t-test for H_0: μ_{UDCA}(change from baseline) = $\mu_{placebo}$(change from baseline)

C.3. Reviewer's Evaluation

C.3.1 Comment on sample size and power estimation

The sponsor's sample size determination is based on normal approximation test of difference in proportion of treatment failure including doubling of total bilirubin as one of the criteria. The sample is only large enough for detecting a 50% reduction of treatment failure assuming the failure rate in placebo is about 40 to 50 percent. With less than 90 patients per treatment group, the study does not have enough power to detect 50 % reduction when the rate in placebo is less than 40%. For example, for all failures excluding doubling of total bilirubin or voluntary withdrawal, the rate in the

placebo group is 21%, with less than 90 patients per group, the power of normal approximation test for detecting a reduction of 25% (i.e. rate of UDCA is 16%) is approximately 22% only. Life table analysis provides higher power when the time to event was longer in the UDCA group.

Table 13 Sample Size and Power (2-sided test)

OUTCOME	PLACEBO RATE (%)	REDUCTION (%)	SAMPLE SIZE/GROUP	POWER (%)
All Failure	40	35	176	80
		45	103	80
		50	82	80
	50	35	124	80
		45	73	80
		50	58	80
Death/Liver Transplant	15	35	617	80
		45	353	80
		55	223	80
	20	35	441	80
		45	253	80
		55	160	80

C.3.2. Comments on the Primary outcomes

For the primary outcome defined in the protocol as treatment failure, the data of this study shows the efficacy of the UDCA treatment in reduction of percentage of treatment failure and in improving the length of time to all treatment failures. The efficacy in prolonging the time to failure is also shown in each of the high and low baseline total bilirubin category and in each of the low and high histologic stages.

However, with the more solid clinical outcomes of death and liver transplant, this study does not provide enough evidence of efficacy in frequency of incidence. In the analysis of the time to death/liver transplant, the estimates of mean time to death/liver transplant are biased toward overestimation because that a large number of patients are censored at the end of the study. Both of the log rank test and Wilcoxon may be biased because of the unequal censoring of the two treatment groups. The comparison is also biased toward null hypothesis that there is no difference in mean time to death/liver transplant between the placebo and the UDCA groups for two reasons. First, the higher censoring

rate at earlier time leads to less cases of death/liver transplant than it should have in the placebo group. Secondly, most of the censored cases are due to the other causes of treatment failure that correlates with death/liver transplant. Both of the reasons may lead to overestimation of the time to death/liver transplant in the placebo group. Bias in Cox regression is also likely biased toward null hypothesis. However, it may also be effected otherwise when the relationships of censoring pattern with the covariate, Mayo risk score are different in the two treatment groups.

C.3.3. Comments on the secondary outcomes

The sponsor's analysis shows that hepatic biochemical markers are improved in patients treated with UDCA and the improvement is consistent in all markers. If the analysis were adjusted for multiple outcomes comparison, the improvement would still be significantly greater than that of the placebo group in alkaline phosphatase, SGOT, total bilirubin, and IgM.

Analysis of the changes from baseline in biliary bile acids are reported without adjustment for multiple outcome comparison. If the p-values were adjusted, they would still be less than 0.01 in ursodeoxycholic and cholic.

D. Mayo Clinic Study Open Label Phase

D.1 Study description

The long-term open-label follow-up study was carried out based on FDA's recommendation. It was prompted by the factors including

1). Request by the FDA to revise the definition of treatment failure by excluding the reasons of doubling of bilirubin and voluntary withdrawal;

2). Request by the FDA in additional analyses relating to the development of varices;

3). Recommendation by one of the principal investigator to include the Mayo risk score as possible covariate in the survival analysis modeling.

Patients who participated in the Mayo Clinic Clinical Trial were offered the option to switch to the open label UDCA treatment after the 132nd patient completed a 2 year treatment in the clinical trial. The study was concluded in 1995 with the patients in the cohort exposed to the active treatment up to 7 years. The UDCA treatment cohort consisted of 91 patients with active treatment up to 7 years continuously and the control cohort consisted of patients started with the placebo control with the option to receive UDCA treatment after at least 2 year of placebo treatment. The study was prompted

with the factors that

A revised definition (as recommended by the FDA) of treatment failure consisted of the following events

1). Death or liver transplant;
2). Histologic progression by 2 stages or to cirrhosis;
3). Development of ascites or encephalopathy or varices- absent from baseline;
4). Inability to tolerate the drug/adverse event;
5). Marked worsening of fatigue or pruritus.

Note that in the revised definition, doubling of total bilirubin and voluntary withdrawal from study were not considered to be treatment failure.

D.2 Sponsor's Analysis of Primary Outcomes

D.2.1 Analysis of Time to Death or Liver Transplantation

The analysis of time to death or liver transplant are summarized in the following table. There is no significant difference in time to death or liver transplantation between the UDCA and the placebo groups in the double-blind phase. In the open label phase, the UDCA group had longer time to death or liver transplant but the difference is only near significant. The life table comparisons performed using both the rank test and the Wilcoxon test have consistent results.

Since the Mayo risk score at baseline is highly associated with the outcome of death and liver transplant, a more powerful comparison on time to death or liver transplant is also performed using Cox proportional hazard model with Mayo risk score as covariate entered into the model. With Cox proportional hazard model, the UDCA treatment in the open label phase has significantly (p=0.007) longer time to death or liver transplant than the placebo group.

Table 14 Time to Death or Liver Transplantation/Mayo Study Open Label Phase

	DOUBLE BLIND PHASE			OPEN LABEL PHASE		
	PLACEBO	UDCA	P-VALUE	PLACEBO	UDCA	P-VALUE
n	86	86		91	89	
Died or Transplanted n (%)	11(13)	6(7)	0.11[a] 0.15[b]	21(23)	13(15)	0.0597[a] 0.0778[b]
Mean Days to Death/Transplant (Std)	707(10.1)	732(18.5)		1405(30.3)	1445(48.5)	

	DOUBLE BLIND PHASE			OPEN LABEL PHASE		
	PLACEBO	UDCA	P-VALUE	PLACEBO	UDCA	P-VALUE
n	90	87		90	87	
Mean (Std)	5.0(1.1)	5.1(1.1)	0.60[c]	5.0(1.1)	5.1(1.1)	0.60[c]
Treatment Comparison			0.07[d]			0.007[d]
Mayo Risk Score			0.0001[d]			0.0001[d]
Treatment by Mayo Risk Score Interaction			0.27[d]			0.28[d]

a: log rank test for H_0: $\mu_{Active} = \mu_{Placebo}$
b: Wilcoxon test for H_0: $\mu_{Active} = \mu_{Placebo}$
c: t test for H_0: $\mu_{Active} = \mu_{Placebo}$
d: Cox proportional hazard model: testing for ratio of hazard rates =1.

D.2.2 Analysis of Time to Treatment Failure

The life table analysis of time to failure is summarized in the table. Statistical significant treatment group difference is found in both the double-blind phase (p=0.01) and in the open label phase (p=0.0001). The results favor the UDCA group in the 2-year double-blind phase and in the open-labeled follow-up phase. When the comparisons are performed using the Wilcoxon's test, p-values are slightly increased.

Table 15 Time to Treatment Failure/Mayo Study Open Label Phase

	MAYO CLINICAL TRIAL			EXTENDED OPEN LABEL STUDY		
	PLACEBO	UDCA	P-VALUE	PLACEBO	ACTIVE	P-VALUE
n	86	86		91	89	
Treatment Failure n (%)	26(30)	17(20)	0.01[a] 0.03[b]	46(51)	29(33)	0.001[a] 0.002[b]
Mean Days to Treatment Failure (Std)	713(19.8)	823(23.3)		1229(63.6)	1497(54.6)	

a: log rank test for H_0: $\mu_{Active} = \mu_{Placebo}$
b: Wilcoxon test for H_0: $\mu_{Active} = \mu_{Placebo}$

D.2.3 Sponsor's Analysis of Secondly Endpoints

The life table analysis of time to varices are summarized in Table 15. Both the log rank test and the Wilcoxon test show statistical significance in treatment group difference in favor of UDCA. In open label phase, p=0.003 based on the log rank test and p=0.004 based on the Wilcoxon test. While in the double-blind phase, p=0.04 based on the log rank test and p=0.07 based on the Wilcoxon test.

Table 16 Time to Varices (in patients without varices at baseline/Mayo Study Open Label Phase

	MAYO CLINICAL TRIAL			EXTENDED OPEN LABEL STUDY		
	PLACEBO	UDCA	P-VALUE	PLACEBO	ACTIVE	P-VALUE
n	67	68		69	70	
Treatment Failure n (%)	9(13)	6(9)	0.04[a] 0.07[b]	20(29)	8(11)	0.003[a] 0.004[b]
Mean Days to Treatment Failure (Std)	757(11.6)	885(21.7)		1503(64.3)	1704(40.8)	

a: log rank test for H_0: $\mu_{Active} = \mu_{Placebo}$
b: Wilcoxon test for H_0: $\mu_{Active} = \mu_{Placebo}$

D.3 Reviewer's Evaluation

D.3.1 Comments on the study design

The open label phase was carried out upon the recommendation of the FDA as an open label study such that some patients might switch to UDCA treatment after the completion of two-year placebo. Hence it is not in the form as a randomized double-blind trial and the results of this study should be interpreted with caution. In Mayo Study, the results of the open label phase are consistent with those obtained in the two-year double blind phase. However, with longer length of the open label phase, the study has more power to show the statistical significance .

D.3.2 Comments on the Primary Endpoints

After adjustment for Mayo risk score at baseline, this study did provide evidence that the UDCA treated patient had significantly prolonged time to death or liver transplant in comparison to the placebo group. As pointed out in the comment on the life table and Cox regression analyses using data in the double blind phase, the p-value is likely biased toward the null hypothesis because of the unequal nonrandom censoring patterns in the two groups of patients. Under an unlikely situation, the censoring-covariate correlation may differs in the two treatment groups in such a way that heavy censoing occures in the high Mayo risk score patients in the UDCA group while the heavy censoing occures in the low Mayo risk score patients in the placebo patients. Under such a censoring pattern, the result of Cox regression may be biased against null hypothesis.

This study also provided evidence that the UDCA treatment prolonged time to treatment failure (all failures except voluntary withdrawal and doubling total bilirubin) at the end of

the double blind phase as well as in open label phase.

The consistency of the results of the double blind phase and open label phase is shown in Figures A to H.

D.3.3 Comments on Secondary Endpoints

This study provides evidence that among the 139 patients without varices at baseline those patients who received the UDCA treatment (n=70) has longer time to varices than those received the placebo treatment only (n=69).

E. Heathcote Clinical Trial

E.1 Study Protocol and Outcome Measures

This multicenter, randomized, double-blind placebo-controlled clinical trial was conducted in Canada. It was a two-year clinical trial involving 11 centers. The patients in the UDCA treatment received daily two to five capsules (depending upon body weight, 14mg/kg/day), each containing 250 mg of UDCA. The study started in April 1988 and completed in July 1992.

This study was designed to assess the therapeutic effect of a 2-year treatment of UDCA in patients with PBC. The primary objective was to compare the UDCA group with the placebo group on the percentage rise in serum bilirubin in two years.

The secondary outcomes to be compared are

1) clinical chemistry which includes total serum bile acids, alkaline phosphatase (ALP), aspartate and alanine transaminases (AST and ALT), gamma-glutamyl transferase (γGT) and total serum cholesterol, serum albumin and immunoglobulin levels, hemoglobin, platelet count and prothrombin times.
2) signs and symptoms of PBC including fatigue, pruritus, ascites, xanthelasma, and encephalopathy.
3) histologic stages at the end of two year treatment.
4) death or liver transplant.
5) toxicity, safety and tolerability to treatment.

Patients were stratified at baseline according to whether they were symptomatic or asymptomatic. They were considered symptomatic if they had a) any pruritus b) any jaundice c) fatigue combined with either pruritus or jaundice or d) xanthelsma combined with either pruritus or jaundice. Two hundred and twenty two patients were enrolled and randomized equally into UDCA or placebo treatment group. Ninety-eight (88.3%)

patients receiving UDCA and 97 (87.4%) receiving placebo were symptomatic.

The study consists of three phases

1). Screening/eligibility phase -
Patients were randomized into the study with the following inclusion and exclusion criteria

Inclusion criteria: patients with positive serum antimitochondrial antibody titer (AMA titer $\geq$ 1:20), serum alkaline phosphatase above the upper limit of normal of the local laboratory, liver biopsy compatible with PBC, and age over 18 years.

Exclusion criteria: patients on active transplant list, taking enzyme-inducing drugs, in pregnancy and those presenting with a severe co-morbid condition which was likely to effect their survival within five years of entry into the trial.

Those patients satisfied the inclusion criteria but treated with other medications for the treatment of PBC were required to complete a three-month wash-out period before inclusion into the trial.

2). Baseline phase -
Patients with well-defined PBC who were AMA positive and had elevated serum alkaline phosphatase were enrolled. Complete clinical and laboratory assessments were performed. Based on the results of baseline assessment, patients were stratified as symptomatic or asymptomatic.

3). Treatment phase -
After treatment started, a physical exam, hematology, immunology and biochemistry parameters, and measurements of serum bile acids were repeated every three months. Weekly records of pruritus, antipruritus medication, energy level, cholestyramine packets and complaints were collected.

Sample size of the trial was determined based on normal approximation test for the comparison of two proportions. The background rate was that without treatment 47% PBC patients would be expected to have a minimum of 50% increase in total serum bilirubin in two years. In order to detect a UDCA treatment effect with at least a reduction from 47% to 23.5% (50% reduction), it would require 85 patients per group (α=0.05, β =0.20). Taking into account that an interim analysis was proposed at 33 month (when half of the patients completed two year treatment), the sample size was increased to 101 patients per group, or 202 in total. Eight of the 11 centers had less than 10 patients (minimum 3 to maximum 8) in each treatment. Three centers with each had more than 15 patients (minimum 16 to maximum 26) in each treatment group consisted of more than 50% of all patients (See also Table A8 in Appendix). The patient flowchart is given below.

Table 17 Patient Flowchart/Heathcote Study

VISIT MONTH	NUMBER OF PATIENTS TREATED IN (%) AT VISIT	
	PLACEBO	UDCA
0	111(100)	111 (100)
3	106(95)	106(95)
6	102(92)	103(93)
9	97(87)	99(89)
12	89(80)	98(88)
18	82(74)	95(86)
21	81(73)	93(84)
24	77(69)	89(80)

There is no obvious difference among the centers in patient flow chart.

E.2 Sponsor's Analysis

Patients in this trial ranged in age from 27.5 to 79 years at study entry. The comparability of the two groups in baseline demographics and information is summarized in Table A9 (Appendix). They are comparable in demographics, symptoms, serum bilirubin and histology stage. There is no obvious difference in baseline information among the 11 centers.

The distribution of concomitant medications during the treatment is similar between the placebo and the UDCA groups with the exception of anti-anxiety medications. Anxiolytic use is significantly higher in the UDCA group ($p<0.005$ with chi-square test).

E.2.1 Analysis of Primary Outcome

The hypothesis that the UDCA treatment reduces the proportion of patients with a more than 50% increase in total bilirubin is tested with the Mantel-Haenszel Chi-square test. The UDCA group has 9% (9.43% vs. 18.85%) less patients than the placebo group experienced more than 50% increase in total bilirubin. The difference was statistically significant ($p<0.001$). The result is also confirmed by comparing the mean % change in bilirubin from baseline measurement. In contrast to a 57.25% increase in the placebo group, the UDCA group has a 2.45% decrease. This difference is statistically significant with both the t-test and the Wilcoxon test ($p=0.0001$). The UDCA effect is also confirmed in patients with baseline histologic stage I and II ($p=0.003$ with the t-test, $p=0.0001$ with the Wilcoxon rank test), in patients with histologic stages III and IV ($p=0.002$ with the t-test, $p=0.0001$ with the Wilcoxon rank test), in patients with symptom stages I and II at baseline ($p=0.0001$ with the t-test and the Wilcoxon rank test). The difference between the treatment groups is not significant in patients with symptom stages III and IV at baseline because of small sample sizes ($n=13$ in UDCA and $n=14$ in placebo). The effect is maintained throughout the study as the UDCA group had lower median and mean serum bilirubin than the placebo group at each visit after three month of treatment.

As shown in the table below, reduction of bilirubin in the UDCA group is observed consistently in all centers except centers 7 and 8. In center 7, the UDCA group has an average increase of 47.66% with the median equals to 55.32 percent, while the placebo group has an avearge decrease of 20.02% with the median equals to -21.43%. In center 8, both the UDCA and the placebo groups have a moderate increases (mean= 52.24% and median=0.00 in the UDCA, mean= 34.14% and median= 22.50% in the placebo). The differences in centers 7 and 8 are not significant.

Table 18 Analysis of Total Bilirubin Change from Baseline/Heathcote Study

MEASUREMENT	PLACEBO n=104	UDCA n=106	UDCA-PLACEBO P-VALUE
> 50% increase n (%)	30 (28.85)	10 (9.43)	< 0.001[a]
≤ 50% increase	74 (71.75)	96 (90.57)	
Median percentage change	20.00%	-17.34%	0.0001[b]
Mean percentage change (std)	57.25 %(117.20%)	-3.45% (73.62%)	0.0001[c]

a: Mantel-Haenszel Chi-square test
b: Wilcoxon rank test
c: t-test

E.2.2 Analysis of Secondary Outcomes

Laboratory Measurements -

Analysis of percentage changes from baseline of laboratory measurements including ALP, AST, ALT, total cholesterol, IgM, IgA, IgG are summarized in Table 19. Comparisons of the mean changes from baseline of the two treatment groups are carried out using the Wilcoxon test and the t-test. The UDCA group has significant reduction from baseline in ALP, AST, ALT, total cholesterol, IgM and IgA (both Wilcoxon signed rank test and paired t-test p-value ≤ 0.001). The reductions in the UDCA group are also significantly different to the changes in the placebo group in ALP, AST, ALT, total Cholesterol, IgM (both Wilcoxon rank test and t-test p-values ≤ 0.0002). There is no significant difference between the UDCA and the placebo groups in changes in IgA and IgG. The UDCA effect is also shown in each center, in patients stratified by baseline histologic stage and by baseline symptom status.

Table 19 Percentage change from baseline in laboratory measurements/Heathcote Study

VARIABLE		PLACEBO (%)	UDCA (%)	P-VALUE
ALP	Median	2.84	-42.43	
	Mean(std)	11.51(42.37)	-38.07(29.02)	0.0001[a] 0.0001[b]
	n	106	106	
AST	Median	4.55	-40.54	
	Mean(std)	9.66(40.64)	-33.50(38.50)	0.0001 0.0001
	n	106	105	

VARIABLE		PLACEBO (N)	UDCA (N)	P-VALUE
ALT	Median	-5.77	-47.60	
	Mean(std)	-0.99(43.39)	-37.85(44.79)	0.0001 0.0001
	n	105	106	
Cholestrol	Median	1.48	-14.69	
	Mean(std)	5.27(27.78)	-14.64(17.54)	0.0001 0.0001
	n	103	101	
IgM	Median	0.79	-18.46	
	Mean(std)	6.02(30.09)	-12.94(36.40)	0.0001 0.0001
	n	88	94	
IgA	Median	12.50	8.86	
	Mean(std)	13.72(21.35)	17.20(34.10)	0.42 0.70
	n	88	94	
IgG	Median	5.21	-1.27	
	Mean(std)	5.52(18.71)	4.04(24.01)	0.64 0.12
	n	88	94	

a: t-test
b: Wilcoxon rank test

Changes in clinical symptoms -

There is no significant difference in the percentages of symptoms (including fatigue, pruritus, xanthelasma, ascites, encephalopathy and jaundice) changes from baseline between the UDCA and the placebo group. The analysis is carried out using the Fisher's Exact test.

Progression of hepatic pathology -

There is no significant difference in the percentages of patients who had progression in fibrosis, acute necrosis, duct paucity, lobular necrosis, locular inflamation, periportal balloning, mallory bodies, neutrophil progression, lympo-plasmacytic and ductular proliferation between the two groups.

Post-hoc defined treatment failure -

A patient is defined post-hoc as a treatment failure if any of the following is true:
1) The patient discontinued the study for any reason;
2) The patient's total bilirubin was greater than or equal to 1.5 mg/dl, or rose to the level that was equal to or greater than two times the baseline level;
3) The patient developed ascites;
4) The patient developed encephalopathy.

The treatment failures of the two groups are compared in the percentage of failures using the Fisher's Exact test and in time-to-failure using the life table analysis with both the log rank test and the Wilcoxon test. The rate of treatment failure is significantly lower in the UDCA group than the placebo group (41.4% vs. 65,8%, $p < 0.001$). The UDCA group has also significantly longer time to treatment failure than the placebo with the mean difference being 3.6 months (p=0.001 long rank test, 0.007 Wilcoxon test).

All comparisons are also made with patients stratified by total bilirubin at baseline and histologic stage. In all strata, the UDCA group had consistently lower treatment failure rate than the placebo group.

E.3 Reviewer's Evaluation

The study design is adequate as a double-blind, randomization clinical trial with approprite sample size and power for its primary objective. Heathcote study is the earliest study designed to evaluate the treatment efficacy of UDCA. The study provides adequate evidence for its primary objective that UDCA treatment reduces the rate of the doubling of total serum bilirubin and reduces the total serum bilirubin at two years. It also provides evidence for the UDCA effect on an post-hoc outcome 'treatment failure' (including withdrawal from study, greater than or equal to .1.5 mg/dl, or doubling in total serum bilirubin, development of ascites and development of encephalopathy).

F. Overall Summary and Recommendation

Primary Endpoints:

The Mayo Clinical Study Double Blind Phase shows that the UDCA treatment (Ursodeoxycholic Acid, 250 mg) reduces the incidence rate of and prolongs the time to overall treatment failure (including death, liver transplantation, histologic progression by two stages or to cirrhosis, development of varices, ascites or encephalopathy, doubling of total bilirubin, marked worsening of fatigue or pruritus, inability to tolerate the drug and voluntary withdrawal) in patients with primary biliary cirrhosis. The study also provided evidence that the UDCA treatment reduces the incidence rate of and prolongs

time to overall treatment failure excluding the doubling of total bilirubin and voluntary withdrawal.

The Mayo Study Open-Label Phase shows that the UDCA treatment (including patients treatment with UDCA after two year placebo treatment) reduces the incidence rate of and prolonged the time to death and liver transplant in patients with primary biliary cirrhosis. The open label phase data confirms also the findings on overall treatment failure in the double blind phase.

The Heathcote Study shows that the UDCA treatment reduces the incidence rate of and prolong the time to the doubling of total serum bilirubin.

Secondary Endpoints

The Mayo Clinical Study Double Blind Phase shows the adequate evidence that the UDCA treatment reduces the incidence rate of the development of any of the symptoms (including cirrhosis, ascites, varices, portal system, encephalopathy, pruritus, fatigue). It also shows that the efficacy of UDCA treatment in the improvement in hepatic biochemical parameters including alkaline phosphatase, GOT, total bilirubin, prothrombin time, IgM, IgA, IgG and gamma globulin. The treatment effect of the UDCA treatment is also shown in the improvement in Mayo risk factor and biliary bile acids including ursodexoxycholic, cholic, chenodeoxycholic, lethoholic.

The Mayo Study Open-Lable Phase shows the effect of the UDCA treatment in prolonging the time to the development of varices.

The Heathcote Study show that the UDCA treatment improves the clinical chemistry including ALP, AST, ALT, IgM and total cholestrol.

/S/ [redacted]
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Concur:

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APPENDIX

Table A1 Baseline Information: Demographics/Mayo Study Double Blind Phase

DEMOGRAPHICS	PLACEBO n	UDCA n
Number enrolled	91	89
Male: number(%)	12 (13)	7 (8)
Age: mean (SD)	51.5 (9.3)	53.6 (9.5)
Height in cm: mean (SD)	164.4 (8.5)	162.9 (5.7)
Weight in kg: mean (SD)	66.7 (12.1)	64.0 (11.8)

Table A2 Baseline Information: Symptoms of Pruritus, Fatigue and Duration of Diagnosis?Mayo Study Double Blind Phase

SYMPTOM AND DURATION	PLACEBO	UDCA
Pruritus: n (%)	48 (52.7)	47(52.8)
Mean Duration in Days (SD)	44.5(37.9)	36.5(37.5)
Jaundice: n (%)	13 (14.3)	12 (13.5)
Mean Duration in Days (SD)	31.0(29.4)	23.6(27.3)
PBC Dx: Mean Duration in days (SD)	43.9(54.7)	39.2(51.6)

Table A3 Baseline Information: Surgical History/Mayo Study Double Blind Phase

SURGICAL HISTORY	PLACEBO n(%)	UDCA n(%)
Portal Shunt	3(3)	0(0)
Cholecystectomy	14(15)	14(16)
Other Abdominal Surgery	38 (42)	37(42)
Mastectomy	4(4)	2(2)
Other Surgery	43(47)	40(45)

Table A4 Baseline Information: Etiological Factors/Mayo Study Double Blind Phase

ETIOLOGICAL FACTORS	PLACEBO n(%)	UDCA n(%)
Family History of Liver Diseases	11(12)	11(13)
History of Hepatitis	9(10)	15(17)
Past Use of Alcohol - Social	29 (33)	29(33)
Past Use of Alcohol - Excess	2(2)	3(3)
Present Use of Alcohol	9 (10)	12(13)
Femal at Child-Bearing Age	29(32)	20(22)
Post-Menopausal	33(36)	34(38)
Hysterectomy	18(20)	29(33)
Phenothiazine	0(0)	1(1)
Estrogen	19(21)	23(20)
Oral Contraception	21(23)	21(24)
Arsenicals	0(0)	0(0)
Cholestatic Drugs	0(0)	0(0)
Methyl Testosterone	0(0)	0(0)

Table A5 Baseline Information: Pharmacologic Treatment 3 Month Prior to Entry?Mayo Study Double Blind Phase

ETIOLOGICAL FACTORS	PLACEBO n(%)	UDCA n(%)
Steroids	14(15)	15(17)
Azathioprine	1(1)	2(2)
Questran	27 (30)	21(23)
Barbiturates	1(1)	1(1)
D-Penticillamine	8 (9)	12(13)
Cyclosporine	5(5)	3(3)
Colchicine	11(12)	6(7)
Other Drugs	52(57)	41(47)
Drug Allergy	37(41)	27(30)

Table A6 Baseline Information: Histologic Stage/Mayo Study Double Blind Phase

STAGE OF DISEASE	PLACEBO (n)	UDCA (n)
I	3(3)[a]	7(8)
II	22(25)	23(27)
III	36(41)	31(36)
IV	26(30)	25(29)

a: p=.57 with Chi-squared test for H_0: P_{UDCA} (stage I) = $P_{placebo}$(stage I)

Table A7 Summary of Treatment Failures/Mayo Study Double Blind Phase

STUDY ENDPOINT	PLACEBO (n)	UDCA (n)	P-VALUE[1] UDCA vs PLACEBO
Patients Received Treatment	86	86	
All Failures	40(47)	20(23)	24 (<.01)
Drug Toxicity[2]	0(0)	0(0)	0(>0.99)
Death	6(7)	3(3)	4(0.50)
Voluntary Withdrawal	11(13)	6(7)	6(0.31)
Transplantation	5(6)	3(3)	3(0.72)
Doubling of Total Bilirubin	11(13)	2(2)	9(0.01)
Worsening of Symptom	2(2)	2(2)	2(>0.99)
Development of Varices	8(9)	6(7)	2(>0.99)
Development of Ascites	4(5)	0(0)	5(0.12)
Development of PSE	1(1)	0(0)	1(>0.99)
Histologic Progress	7(8)	6(7)	1(0.81)

[redacted]	[redacted]	[redacted]	
First Reason for Failure[3]			
Drug Toxicity	0(0)	0(0)	0(>0.99)
Death	6(7)	2(2)	5(0.28)
Voluntary Withdrawal	10(12)	6(7)	5(0.43)
Transplantation	4(5)	3(3)	2(>0.99)
Doubling of Total Bilirubin	12(14)	2(2)	12(0.01)
Worsening of Symptom	2(2)	3(3)	-1(>0.99)
Development of Varices	5(6)	6(7)	-1(>0.99)
Development of Ascites	4(5)	0(0)	5(0.12)
Development of PSE	1(1)	0(0)	1(>0.99)
Histologic Progress	6(5)	5(6)	1(>0.99)

1: Fisher's Exact Test
2,3: Patients were counted more than once if they were classified as treatment failure for more than one reason.

Table A8 Distribution of Patients by Center/Heathcote Trial

CENTER	PLACEBO (n=111)		[redacted] (n=111)	
	n	%	n	%
1	24	21.6	2	23.5
2	17	15.3	16	14.4
3	9	8.1	8	7.2
4	26	23.5	23	20.7
5	5	4.5	6	5.4
6	4	3.6	3	2.7
7	4	3.6	4	3.6
8	8	7.2	8	7.2
9	6	5.4	7	6.3
10	3	2.7	4	3.6
11	5	4.5	6	5.4

Table A9 Baseline Information/Heathcote Trial

Male n	6	10
Age Mean (std)	55.4 (12.9)	57.3 (10.5)
Weight in kg Mean (std)	62.4 (11.8)	65.0 (13.0)
Symptoms		
Fatigue n (%)	83 (74.8)	87 (78.4)
Pruritus n (%)	79 (71.2)	87 (78.4)
Xanthelasma n (%)	12 (10.8)	20 (18.0)
Ascites	4 (3.6)	2 (1.8)
Variceal Bleeding	9 (8.1)	7 (6.3)
Bilirubin n	111	109
Median, Mean (std)	18, 30.7 (38.6)	19, 39.6 (64.1)
Histologic Stage		
n	108	108
I n (%)	20 (18.5)	19 (17.6)
II n (%)	27 (25.0)	31 (28.7)
III n(%)	33 (30.6)	29 (26.9)
IV n(%)	28 (25.9)	29 (26.9)

APPEARS THIS WAY ON ORIGINAL