CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-797

21-798

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#:	21-797
DRUG NAME:	Baraclude[0] (Entecavir)
INDICATION:	Treatment of Chronic Hepatitis B Infection
TYPE OF REVIEW:	Clinical
APPLICANT:	Bristol-Myers-Squibb
DATES:	Oct, 2004 - March, 2005
REVIEW PRIORITY:	Priority
BIOMETRICS DIVISION:	Biometrics 3
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STATISTICAL REVIEW AND EVALUATION

NDA#: 21-797

1. Executive Summary

The applicant submitted four randomized, controlled pivotal clinical trials with entecavir for this application: trial 14, originally planned as a phase 2 study, and trials 22, 26, and 27, all phase 3 trials. Two of the trials, 14 and 26, enrolled subjects who were refractory to LVD, defined as either HBV DNA > 5 log copies/mL while on LVD or evidence of LVD^R substitutions in the viral DNA. For these subjects, a dose of 1 mg qd entecavir (ETV) was used. The other two trials, 22 and 27, enrolled subjects who were nucleoside naive (fewer than 12 weeks of treatment). Trial 22 recruited HBeAg+ subjects; trial 27 recruited HBeAg-/HBeAb+ subjects. For these subjects, a dose of .5 mg qd entecavir was used. The control subjects in all trials received 100 mg qd of lamivudine (LVD).

The trials were planned as superiority trials in the LVD experienced populations and as non-inferiority trials in the LVD naive populations. All trials compared proportions of subjects with HBV DNA below limit of quantitation (BLQ) at the final visit (week 24 for trial 14 and week 48 for the three planned pivotal trials). This was the primary endpoint in trial 14 and a secondary endpoint in trials 22, 26, and 27. The latter three trials compared proportions of subjects with Knodell necrosis score improving by at least two points between baseline and week 48 biopsies.

In all four trials, subjects on ETV had statistically and clinically superior responses to subjects on LVD. This was even true in the two trials intended as non-inferiority trials. The ETV superiority was demonstrated for both primary endpoints, improvement in Knodell necrosis score, and secondary endpoints, suppression of HBV DNA to BLQ and suppression of ALT to below upper limit of normal (ULN). These findings were robust to sensitivity analyses conducted on the missing data.

The applicant also submitted a small trial, trial 38, in which HBV and HIV co-infected patients were enrolled. The findings on primary and secondary endpoints were compatible with those in trials 14, 22, 26, and 27. Because the sample size in this trial was small, no treatment effects were statistically significant. Details on the review of this trial are not

reproduced here.

The FDA statistical reviewer concludes that the applicant has established that entecavir is an effective treatment of hepatitis B, at a dose of 1 mg qd in LVD refractory subjects and at a dose of .5 mg qd in LVD naive subjects.

2. Introduction

2.1 Overview

The applicant submitted four randomized, controlled pivotal clinical trials with entecavir for this application: trial 14, a phase 2 study, and trials 22, 26, and 27, all phase 3 trials.

2.2 Data Sources

2.2.1 Objectives in Trials

The primary objective of study 14 was to compare the efficacy of three doses of entecavir (ETV) (.1, .5 and 1 mg qd) to that of lamivudine (LVD) at 100 mg qd in LVD refractory patients.

In trial 14, the primary efficacy endpoints were 1) chemical response (ALT < 1.25 ULN (upper limit of normal)), 2) viral response (HBV DNA < 400 copies/mL by PCR assay (or < .7 MEq/mL by BDNA assay)), and 3) serologic response (loss of HBeAg and HBeAb seroconversion), all measured at week 24. Since the study was planned as a dose-ranging phase 2 study, no single endpoint was selected as primary. The study population in trial 14 was HBV infected patients with compensated liver disease, and refractory to LVD, defined as HBV DNA > 5 log copies/mL while on LVD.

The primary objective of studies 22 and 27 was to compare the efficacy of ETV at .5 mg qd to that of LVD at 100 mg qd in nucleoside naive patients.

The primary objective of study 26 was to compare the efficacy of ETV at 1 mg qd to that of LVD at 100 mg qd in LVD refractory patients.

In these three phase 3 trials, the primary efficacy endpoint was change in histology, as determined by biopsies at baseline and at week 48. The chemical, viral, and serological endpoints of trial 14 (but measured at week 48) were secondary endpoints in these trials. The study population in all three trials comprised HBV infected patients with compensated liver disease and evidence

of hepatic inflammation. The study population in trials 22 and 27 was also nucleoside naive (fewer than 12 weeks of treatment). Trial 22 recruited HBeAg+ subjects; trial 27 recruited HBeAg-/HBeAb+ subjects. The study population in trial 26 was refractory to LVD, defined as either HBV DNA > 5 log copies/mL while on LVD or evidence of LVD^R substitutions in the viral DNA.

2.2.2 Summary of Study Design

All four trials were double-blind, randomized, parallel, active controlled, and multinational. In the phase 3 trials, subjects were randomized 1:1 and treated for 52 weeks, with the primary endpoint measured at week 48. Subjects were classified as complete responders, partial responders, or failures on the basis of this endpoint. Partial responders were able to continue blinded treatment until week 96. Complete responders and failures both finished their blinded treatment at week 52. All subjects were also to have follow-up to 24 weeks after the end of treatment.

In the phase 2 trial (trial 14), subjects were randomized 1:1:1:1 and treated for 24 weeks. Viral responders could continue treatment to week 52; non-responders at week 24 were followed for 12 weeks, post-treatment. Partial responders at week 52 could continue treatment to week 76. All subjects treated to week 52 were to be followed for 24 weeks post-treatment.

All four trials were multi-center, multinational trials. The distribution of sites and total treated patients across continents for the four trials is given in table 2.2.2 A below.

TABLE 2.2.2 A
SITES AND PATIENTS BY CONTINENT

TRIAL_14

REGION	SITES	PATS	ETV_.1	_.5	_1	LVD
Asia	8	42	13	11	8	10
Europe	12	79	20	20	21	18
North America	20	60	14	16	13	17

TRIAL_26

REGION	SITES	PATS	ETV	LVD
Asia	22	71	35	36
Europe	25	134	62	72
North America	23	55	31	24
South America	5	26	13	13

TRIAL_22

REGION	SITES	PATS	ETV	LVD
Asia	35	339	172	167
Europe	40	172	84	88
North America	34	102	47	55
South America	17	96	51	45

TRIAL_27

REGION	SITES	PATS	ETV	LVD
Asia	29	210	106	104
Europe	58	304	156	148
North America	23	55	28	27
South America	10	69	35	34

2.2.3 Patient Accounting and Baseline Characteristics

715 patients were randomized in trial 22. Of these, 6 patients never started treatment. Of the 709 eligible patients who started treatment, 48 discontinued treatment before the end of the first year. Table 2.2.3 A summarizes the primary reasons for discontinuation from study 22 and from treatment. Recall that the 24 week follow-up period begins at the end of year 2 for partial responders and at the end of year 1 for complete responders and failures.

TABLE 2.2.3 A
PATIENT STATUS, TRIAL 22

	ETV		LVD	
Randomized	357		358	
In Treated ITT	354		355	
Withdrew 1st Yr		14		34
AE/Death		1		11
LTFU		13		23
LOE		0		0
Complete 1st Yr		340		321
Started 2nd Yr		252		190
Withdrew 2nd Yr		12		41
AE/Death		0		0
LTFU		10		7
LOE		2		34
Continuing 2nd Yr		229		141
Complete 2nd Yr		11		8
Started 24 Wk FU*		97		104
Withdrew 24 Wk FU		7		20
AE/Death		0		3
LTFU		7		17
Complete 24 Wk FU		44		38

* Follow-Up

648 patients were randomized in trial 27. Of these, 10 patients never started treatment. Of the 638 eligible patients who started treatment, 31 discontinued treatment before the end of the first year. Table 2.2.3 B summarizes the primary reasons for discontinuation from study 27 and from treatment.

TABLE 2.2.3 B
PATIENT STATUS, TRIAL 27

	ETV	LVD
Randomized	331	317
In Treated ITT	325	313
Withdrew 1st Yr	14	17
AE/Death	8	9
LTFU	6	8
LOE	0	0
Complete 1st Yr	311	296
Started 2nd Yr	46	61
Withdrew 2nd Yr	6	10
AE/Death	0	0
LTFU	6	6
LOE	0	4
Continuing 2nd Yr	29	35
Complete 2nd Yr	11	16
Started 24 Wk FU*	281	248
Withdrew 24 Wk FU	27	72
AE/Death	0	0
LTFU	26	65
LOE	1	7
Complete 24 Wk FU	164	91

* Follow-Up

293 patients were randomized in trial 26. Of these, 7 patients never started treatment. Of the 286 eligible patients who started treatment, 27 discontinued treatment before the end of the first year. Table 2.2.3 C summarizes the primary reasons for discontinuation from study 26 and from treatment.

TABLE 2.2.3 C
PATIENT STATUS, TRIAL 26

	ETV		LVD	
Randomized	147		146	
In Treated ITT	141		145	
Withdrew 1st Yr		8		19
AE/Death		1		9
LTFU		7		8
LOE		0		2
Complete 1st Yr	133		126	
Started 2nd Yr	91		28	
Withdrew 2nd Yr	10		14	
AE/Death		1		1
LTFU		2		0
LOE		7		13
Continuing 2nd Yr	73		13	
Complete 2nd Yr	8		1	
Started 24 Wk FU*	22		20	
Withdrew 24 Wk FU	4		2	
AE/Death		0		0
LTFU		2		1
LOE		2		1
Complete 24 Wk FU	12		9	

* Follow-Up

Tables 2.2.3 D and E give demographic characteristics, baseline histology, and baseline HBV disease characteristics of the subjects in the four pivotal trials.

182 patients were randomized in trial 14. Of these, 1 patient never started treatment. Of the 181 eligible patients who started treatment, 9 discontinued treatment before the end of 24 weeks. Table 2.2.3 D summarizes the primary reasons for discontinuation from study 14 and from treatment.

TABLE 2.2.3 D
PATIENT STATUS, TRIAL 14

	ETV .1	ETV .5	ETV 1	LVD
Randomized	47	47	42	46
In Treated ITT	47	47	42	45
Withdrew <24 Wks	1	4	2	2
AE/Death	1	2	1	0
Lab Abnorm	0	1	1	0
LTFU	0	1	0	2
Complete 24 Wks	46	43	40	43
Withdrew 24 Wk FU*	14	3	1	16
AE/Death	3	0	0	1
LTFU	0	0	0	1
LOE	11	3	1	14
Complete 24 Wk FU	32	40	39	27

* Follow-Up

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Tables 2.2.3 D and E give demographic characteristics, baseline histology, and baseline HBV disease characteristics of the subjects in the four pivotal trials.

TABLE 2.2.3 D
BASELINE DEMOGRAPHICS BY TRIAL

	Nucleoside Naive Subjects		LVD Refractory Subjects	
	Trial 22	Trial 27	Trial 26	Trial 14
Mean Age	35	44	39	48
Gender				
Male	75%	75%	74%	39%
Female	25%	25%	26%	61%
Race				
Asian	57%	39%	37%	30%
White	40%	58%	62%	63%
Other	3%	3%	1%	7%

TABLE 2.2.3 E
BASELINE HBV DISEASE TRAITS BY TRIAL

	Nucleoside Naive Subjects		LVD Refractory Subjects	
	Trial 22	Trial 27	Trial 26	Trial 14
Knodell Necro-inflammatory Score	7.8	7.9	6.5	NA
Ishak Fibrosis Score	2.3	2.4	2.3	NA
Knodell Fibrosis Score	1.65	1.86	1.73	NA
Mean HBV				
by BDNA[1]	2.59	1.24	2.50	2.45
by PCR[2]	9.66	7.58	9.36	9.18
HBsAg +	100%	100%	100%	100%
HBeAg +	98%	<1%	97%	68%
HBeAb +	3%	99%	4%	28%
Mean ALT	143	142	128	125

[1] log Meq/mL
[2] log copies/mL

2.2.4 Summary of Methods of Assessment

2.2.4.1 Schedule of Measurements

In trials 22, 26, and 27 patients had liver biopsies at baseline and at week 48. In these trials, HBV DNA and ALT were measured at weeks 0, every 4 weeks to week 16, and every 8 weeks to week 72. In trial 14, HBV DNA and ALT were measured at weeks 0, 2, 4, 12, 24, 36, 48, 60, and 76. HBV DNA levels were measured by both the BDNA assay and the PCR assay.

2.2.4.2 Assessment of Treatment Effects

In trial 26, the protocol specified co-primary endpoints at week 48 were

1) histological improvement, defined as >=2 point decrease from baseline in Knodell necroinflammatory score and no increase from baseline in Knodell fibrosis score, and
2) composite endpoint, defined as HBV DNA undetectable by bDNA assay (limit of quantitation, LOQ, = .7 MEq/mL) and normalization of ALT (ALT < 1.25 ULN, upper limit of normal).

A number of secondary endpoints were also used. These were >=1 point improvement in Ishak fibrosis score; reduction from baseline in week 48 hepatic cccDNA, in total hepatic HBV DNA, in hepatic HBcAg, in hepatic HBsAg, and in HBV DNA by PCR assay; HBV DNA <400 copies/mL by PCR; loss of HBeAg; appearance of HBeAb + loss of HBeAg.

Subjects missing their biopsy at baseline (or other baseline covariates) were excluded from the analysis of histologic improvement (or other binary endpoints). Randomization should balance such missing data and preclude biases in such an analysis. Loss to follow-up (missing week 48 biopsy or end of study ALT or HBV DNA data, as opposed to missing baseline data) counted as failure in all of the binary endpoints. The handling of missing values for those secondary endpoints which were ordinal or continuous is not described.

Trials 22 and 27 used the same endpoints as trial 26, except that the composite endpoint was considered secondary, rather than co-primary.

Trial 14, the phase 2 trial, had no histologic data. In this trial, the primary endpoint was HBV DNA below LOQ (.7 MEq/mL) by the bDNA assay at week 24. Secondary endpoints included reduction from baseline in week 24 and week 48 in HBV DNA by PCR assay, HBV DNA <400 copies/mL by PCR, HBV DNA < 2 logs below baseline by each assay, loss of HBeAg, appearance of HBeAb + loss of HBeAg, and ALT normalization.

2.2.5 Summary of Statistical Analysis

In trial 26, the percent successful on each of the two binary endpoints, histologic improvement and virologic/ALT success, were tested for ETV superiority to LVD by unstratified tests. A Bonferroni adjustment was used for multiple endpoints. Superiority on either endpoint was considered a demonstration of efficacy. An analysis stratified by region was performed for exploratory purposes.

In trials 22 and 27, ETV was considered effective if with two-sided 95% confidence ETV was no more than 10% worse than LVD with respect to the percent successful on histologic improvement. The confidence limits for the difference between ETV and LVD in percent successful were computed without stratification. Note that these trials required no adjustment for multiple endpoints.

2.2.6 Summary of Applicant's Results

The reported results in the four pivotal trials are given in tables 2.2.6 A-D. Tables 2.2.6 A, B give the results from the two trials with nucleoside naive subjects, trials 22 and 27, at wee 48; tables 2.2.6 C, D give the results from the two trials with LVD refractory subjects, trial 26 at week 48 and trial 14 at week 24. Notice that in trials 22, 27, and 26, the primary

endpoint and the three individual biopsy scores (Knodell necrosis, Knodell fibrosis, and Ishak fibrosis), a failure is counted for each subject with evaluable baseline and missing week 48 biopsy.

TABLE 2.2.6 A

RESULTS FROM NAIVE SUBJECTS, TRIAL 22

	ETV .5mg		LVD				
Endpoint	N[1]	Mean	N	Mean	Diff.	95% Limits	P-value
Binary Endpoints							
Improve Hist[2]	314	72%	314	62%	9.9%	2.6%, 17.2%	.0085
Improve KNS[3]		74%		64%	9.9%	2.7%, 17.1%	.0077
No Worse KFS[4]		89%		82%	7.6%	2.2%, 13.1%	.0063
Improve IFS[5]		39%		35%	3.2%	-4.4%, 10.7%	.41
Improve Hist[6]	357	64%	358	55%	9.1%	1.9%, 16.3%	.0131
DNA BLQ[7]	354	91%	355	65%	26%	20%, 31%	<.0001
DNA BLQ[8]		69%		38%	32%	25%, 38%	<.0001
Lost HBeAg		22%		20%	2.3%	-3.7%, 8.3%	.45
" + HBeAb Gain		21%		18%	2.9%	-2.9%, 8.7%	.33
ALT <1.25 ULN		78%		70%	8.1%	1.7%, 14.5%	.0136
Changes from baseline							
Hep ccc DNA	159	-.9	146	-.7	-.2	-.3, -.1	.0033
Total Hep DNA		-2.1		-1.6	-.5	-.6, -.3	<.0001
HBV DNA[8]	340	-7.0	324	-5.5	-1.6	-.x, -.x	<.0001

[1] N used to compute endpoint
[2] Primary Endpoint, missing week 48 = failure
[3] Knodell Necroinflammatory Score
[4] Knodell Fibrosis Score
[5] Ishak Fibrosis Score
[6] All subjects, missing baseline = failure
[7] by bDNA assay
[8] by PCR assay

TABLE 2.2.6 B

RESULTS FROM NAIVE SUBJECTS, TRIAL 27

	ETV .5mg		LVD				
Endpoint	N[1]	Mean	N	Mean	Diff.	95% Limits	P-value
Binary Endpoints							
Improve Hist[2]	296	70%	287	61%	9.6%	2.0%, 17.3%	.0212
Improve KNS[3]		73%		64%	9.5%	2.0%, 17.1%	.0130
No Worse KFS[4]		84%		79%	5.7%	-.6%, 12.0%	.08
Improve IFS[5]		36%		38%	-1.8%	-9.7%, 6.0%	.65
Improve Hist[6]	331	63%	317	55%	8.6%	1.0%, 16.1%	.0267
DNA BLQ[7]	325	95%	313	89%	5.9%	1.8%, 10.1%	.0053
DNA BLQ[8]		91%		73%	18%	12%, 24%	<.0001
ALT <1.25 ULN		86%		81%	4.1%	-1.7%, 9.8%	.17
Changes from baseline							
Hep ccc DNA	107	-.5	104	-.5	0	-.2, .1	.5
Total Hep DNA		-1.5		-1.4	-.1	-.2, .0	.07
HBV DNA[8]	314	-5.2	297	-4.7	-.46	-.64, -.29	<.0001

[1] N used to compute endpoint

[2] Primary Endpoint, missing week 48 = failure

[3] Knodell Necroinflammatory Score

[4] Knodell Fibrosis Score

[5] Ishak Fibrosis Score

[6] All subjects, missing baseline = failure

[7] by bDNA assay

[8] by PCR assay

TABLE 2.2.6 C

RESULTS FROM LVD REFRACTORY SUBJECTS, TRIAL 26

	ETV 1mg		LVD				
Endpoint	N[1]	Mean	N	Mean	Diff.	95% Limits	P-value
Binary Endpoints							
Improve Hist[2]	124	55%	116	28%	27.3%	13.6%, 40.9%	<.0001
Composite[2]	141	55%	145	4%	51%	40%, 61%	<.0001
Improve KNS[3]	124	55%	116	32%	23%	10.7%, 35%	.0003
No Worse KFS[4]		87%		70%	16.5%	6.1%, 26.8%	.0020
Improve IFS[5]		34%		16%	17.5%	6.8%, 28.2%	.0019
Improve Hist[6]	147	47%	146	23%	24%	12%, 36%	<.0001
DNA BLQ[7]	141	66%	145	6%	60%	52%, 69%	<.0001
DNA BLQ[8]		21%		1%	19.2%	12.3%, 26.1%	<.0001
Lost HBeAg		10%		3%	6.5%	.7%, 12.2%	.0278
" + HBeAb Gain		8%		3%	5.0%	-.1%, 10.2%	.06
ALT <1.25 ULN		75%		23%	52%	42%, 62%	<.0001
Changes from baseline							
Hep ccc DNA	74	-.6	59	.0	-.6	-.8, -.4	<.0001
Total Hep DNA		-1.7		-.2	-1.4	-1.7, -1.2	<.0001
HBV DNA[8]	133	-5.1	128	-.5	-4.4	-4.8, -4.0	<.0001

[1] N used to compute endpoint

[2] Co-Primary Endpoint, Composite = HBV BLQ + ALT<1.25 ULN confidence limits adjusted to 97.5%, missing week 48 = failure

[3] Knodell Necroinflammatory Score

[4] Knodell Fibrosis Score

[5] Ishak Fibrosis Score

[6] All subjects, missing baseline = failure

[7] by bDNA assay

[8] by PCR assay

TABLE 2.2.6 D
RESULTS FROM LVD REFRACTORY SUBJECTS,
TRIAL 14, WEEK 24

	ETV 1mg		LVD				
Endpoint	N[1]	Mean	N	Mean	Diff.	95% Limits	P-value
Binary Endpoints							
DNA BLQ[2,7]	42	79%	45	13%	65%	40%, 91%	<.0001
DNA BLQ[8]		17%		2%	14.4%	2.3%, 26.6%	.0198
Lost HBeAg	27	11%	32	6%	2.3%	-3.7%, 8.3%	.45
" + HBeAb Gain		4%		0%	2.9%	-2.9%, 8.7%	.33
ALT <1.25 ULN[9]							
at wk 24	28	39%	33	21%	18.1%	-4.9%, 41.0%	.12
at wk 48		68%		6%	62%	38%, 86%	<.0001
Changes from baseline							
HBV DNA[7]	40	-2.4	43	-0.4			<.0001
HBV DNA[8]		-4.2		-1.0			<.0001

[1] N used to compute endpoint
[2] Primary Endpoint
[7] by bDNA assay
[8] by PCR assay
[9] with abnormal baseline ALT

2.2.7 Summary of Applicant's Conclusions

The applicant concluded that .5 mg qd entecavir had demonstrable histologic and antiviral efficacy in nucleoside naive subjects that was at least comparable to lamivudine.

The applicant also concluded that 1 mg qd entecavir had histologic and antiviral efficacy in lamivudine experienced patients that was superior to continuing lamivudine.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Sensitivity Analyses on Biopsy Scores

Table 3.1.1 A shows for the three pivotal trials for both the number of subjects with missing and complete data on change in biopsy results. The missing subjects are broken into two categories, those missing both baseline and week 48 or those missing only week 48. The subjects with complete data are divided into failures and successes according to four histological endpoints: overall improvement, HIST_IMP, (the primary endpoint), improvement in Ishak fibrosis score, ISF_IMP, improvement in Knodell fibrosis score, KSF_IMP, and Knodell necrosis score, KSN_IMP. Both counts and percents are given.

TABLE 3.1.1 A
MISSING AND COMPLETE BIOPSY RESULTS,
WITH NUMBER IMPROVED OR NOT

	Trial_26		Trial_22		Trial_27	
	ETV	LVD	ETV	LVD	ETV	LVD
Missing	31	48	62	86	60	63
Base	17	30	40	41	29	26
Wk_48	14	18	22	45	31	37
Completed	110	98	292	269	265	250
HIST_IMP						
Failed	42	66	66	74	208	174
Success	68	32	226	195	57	76
ISF_IMP						
Failed	68	79	171	158	158	141
Success	42	19	121	111	107	109
KSF_IMP						
Failed	82	89	231	212	211	188
Success	28	9	61	57	54	62
KSF_IMP						
Worse	3	17	11	12	16	25
No Worse	107	81	281	257	249	225
KSN_IMP						
Failed	42	61	61	69	48	67
Success	68	37	231	200	217	183

TABLE 3.1.1 A (cont.)
MISSING AND COMPLETE BIOPSY RESULTS,
WITH PERCENT IMPROVED OR NOT

	Trial_26		Trial_22		Trial_27	
	ETV	LVD	ETV	LVD	ETV	LVD
Missing	22%	33%	17%	25%	19%	20%
Base	12%	21%	11%	12%	9%	8%
Wk_48	10%	12%	6%	13%	10%	12%
Completed	78%	67%	83%	76%	81%	80%
HIST_IMP						
Failed	30%	45%	19%	21%	18%	24%
Success	48%	22%	64%	55%	64%	56%
ISF_IMP						
Failed	48%	54%	48%	45%	49%	45%
Success	30%	13%	34%	31%	33%	35%
KSF_IMP						
Failed	58%	61%	65%	60%	65%	60%
Success	20%	6%	17%	16%	17%	20%
KSF_IMP						
Worse	2%	12%	3%	3%	5%	8%
No Worse	76%	55%	79%	72%	77%	72%
KSN_IMP						
Failed	30%	42%	17%	19%	15%	21%
Success	48%	25%	65%	56%	67%	58%

One can see about a quarter of the subjects in each enrolled arm are missing one of their two biopsy scores, with more missing data in the LVD arm, by 1% to 8%. In the applicant's analysis of histological improvement, subjects with an evaluable baseline biopsy were regarded as failures if their week 48 biopsy was missing. The sponsor also reported a true ITT analysis in which all randomized subjects, even if never treated, were included, with all missing data counting as failures. As a sensitivity analysis, the FDA reviewer compared these results to those in which such subjects were discarded from both numerator and denominator in computing percent successful. The number of successes is the same in all these results but, depending on which subjects are included and counted as failures, the denominators in the percent successful change.

TABLE 3.1.1 A

HISTOLOGIC IMPROVEMENT, VARIOUS DEFINITIONS

ENDPT	MEAN DIFF	95% LIMITS LOWER	UPPER	# Succ/# Arm = % Success ETV	LVD	PVALUE
Trial 22						
A	9.9%	2.6%,	17.2%	226/314=72%	195/314=62%	.0085
B	9.1%	1.9%,	16.3%	226/357=64%	195/358=55%	.0131
C	4.9%	-2.3%,	12.1%	226/292=77%	195/269=72%	.18
D	8.9%	1.7%,	16.1%	226/354=64%	195/355=55%	.0153
Trial 27						
A	9.6%	2.0%,	17.3%	208/296=70%	174/287=61%	.0212
B	8.6%	1.0%,	16.1%	208/331=63%	174/317=55%	.027
C	8.9%	1.3%,	16.4%	208/265=78%	174/250=70%	.021
D	8.4%	0.8%,	16.0%	208/325=64%	174/313=56%	.0298
Trial 26						
A	27.3%	13.6%,	40.9%	68/124=55%	32/116=28%	<.0001
B	24%	12%,	36%	68/147=47%	32/146=23%	<.0001
C	29.2%	16.2%,	42.2%	68/110=62%	32/98=33%	<.0001
D	26.2%	15.5%,	36.8%	68/141=48%	32/145=22%	<.0001

A = Valid baseline, Miss Week 48 = Failure

B = Missing baseline or Never treated = Failure

C = Missing baseline or week 48 = not included

D = Missing baseline = Failure, Never treated = not included

TABLE 3.1.1 B

ISHAK FIBROSIS IMPROVEMENT, VARIOUS DEFINITIONS

ENDPT	MEAN DIFF	95% LIMITS LOWER	UPPER	# Succ/# Arm = % Success ETV	LVD	PVALUE
Trial 22						
A	3.2%	-4.4%,	10.7%	121/314=39%	111/314=35%	.41
C	0.2%	-8.0%,	8.3%	121/292=41%	111/269=41%	.97
Trial 27						
A	-1.8%	-9.7%,	6.0%	107/296=36%	109/287=38%	.65
C	-3.2%	-11.7%,	5.3%	107/265=40%	109/250=44%	.46
Trial 26						
A	17.5%	6.8%,	28.2%	42/124=34%	19/116=16%	.0019
C	18.8%	6.8%,	30.8%	42/110=38%	19/98=19%	.0021

A = Valid baseline, Miss Week 48 = Failure

C = Missing baseline or week 48 = not included

TABLE 3.1.1 C

KNODELL FIBROSIS NO WORSE, VARIOUS DEFINITIONS

ENDPT	MEAN DIFF	95% LIMITS LOWER	UPPER	# Succ/# Arm = % Success ETV	LVD	PVALUE
Trial 22						
A	7.6%	2.2%,	13.1%	381/314=89%	257/314=82%	.0063
C	0.7%	-2.6%,	4.0%	281/292=96%	257/269=96%	.68
Trial 27						
A	5.7%	-.6%,	12.0%	249/296=84%	225/287=79%	.08
C	4.0%	-0.7%,	8.7%	249/265=94%	225/250=90%	.098
Trial 26						
A	16.5%	6.1%,	26.8%	107/124=87%	81/116=70%	.002
C	14.6%	6.5%,	22.7%	107/110=97%	81/98=83%	.0004

A = Valid baseline, Miss Week 48 = Failure

C = Missing baseline or week 48 = not included

TABLE 3.1.1 D

KNODELL NECROSIS IMPROVEMENT, VARIOUS DEFINITIONS

ENDPT	MEAN DIFF	95% LIMITS LOWER	UPPER	# Succ/# Arm = % Success ETV	LVD	PVALUE
Trial 22						
A	9.9%	2.7%,	17.1%	231/314=74%	200/314=64%	.0077
C	4.8%	-2.2%,	11.8%	231/292=79%	200/269=74%	.18
Trial 27						
A	9.5%	2.0%,	17.1%	217/296=73%	183/287=64%	.013
C	8.7%	1.5%,	15.9%	217/265=82%	183/250=73%	.018
Trial 26						
A	23%	10.7%,	35%	68/124=55%	37/116=32%	.0003
C	24.1%	10.9%,	37.3%	68/110=62%	37/98=38%	.0004

A = Valid baseline, Miss Week 48 = Failure

C = Missing baseline or week 48 = not included

The main difference between the analyses is that the percentage of subjects with valid baseline biopsy but missing week 48 biopsy is higher in the LVD arm than in the ETV arm: 12% vs 10% in trial 26 and in trial 27, 13% vs 6% in trial 22. It is only in trial 22 that this difference is large enough for the handling of these incomplete data to matter. The difference in histologic improvement between ETV and LVD is either 10% or 5%, depending on whether the subjects with no week 48 biopsy are

failures or not included in the analysis. The observed improvement in response of ETV relative to LVD is either significant at level .0085 or insignificant (p=.18), depending on the same choices with respect to these subjects. Finding with respect to the components of histological improvement are similar.

Even in trial 22, the difference in conclusions is not large enough to cast doubt on the conclusion of efficacy. Trial 22 was an active control trial. The analysis excluding subjects missing week 48 biopsy may cast doubt on the superiority of ETV to LVD in LVD naive subjects but it does not cast doubt on the superiority of ETV to placebo in these patients.

As an additional sensitivity analysis on the observed difference in histological improvement between ETV and LVD, the FDA reviewer imputed histological improvement scores (yes or no) to all the missing subjects, including those missing baseline values. The proportion of missing subjects who were considered successes ranged from 0% to 100% independently in both arms of each trial. The results of these analyses are given in figures 3.1.2 A, B, and C below.

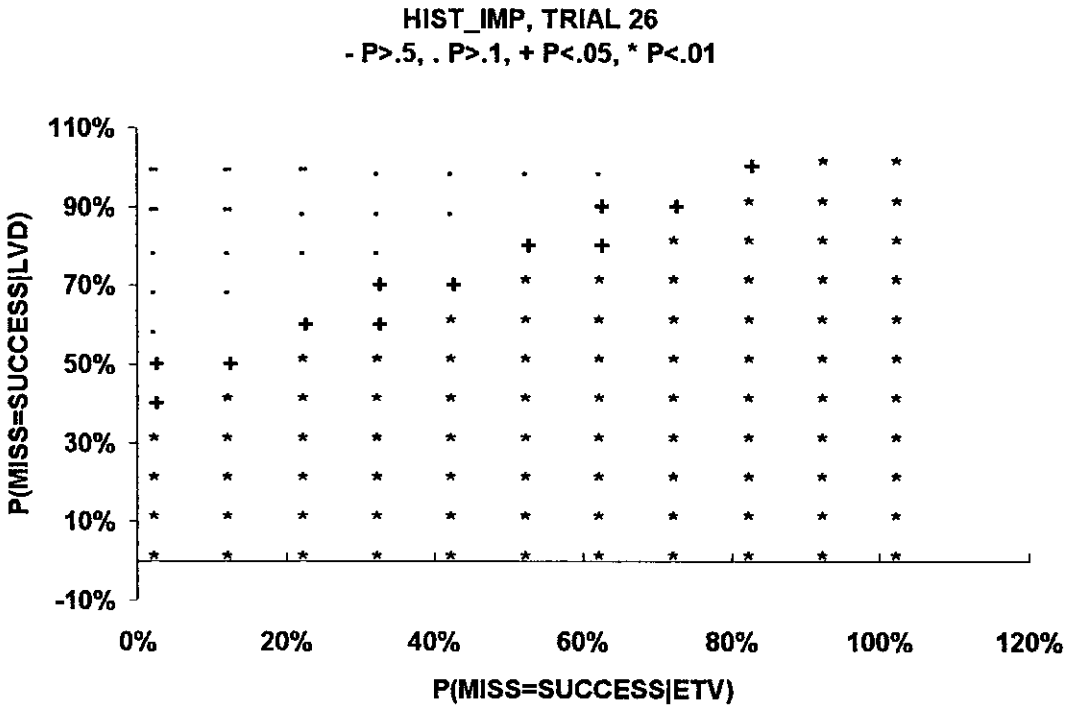

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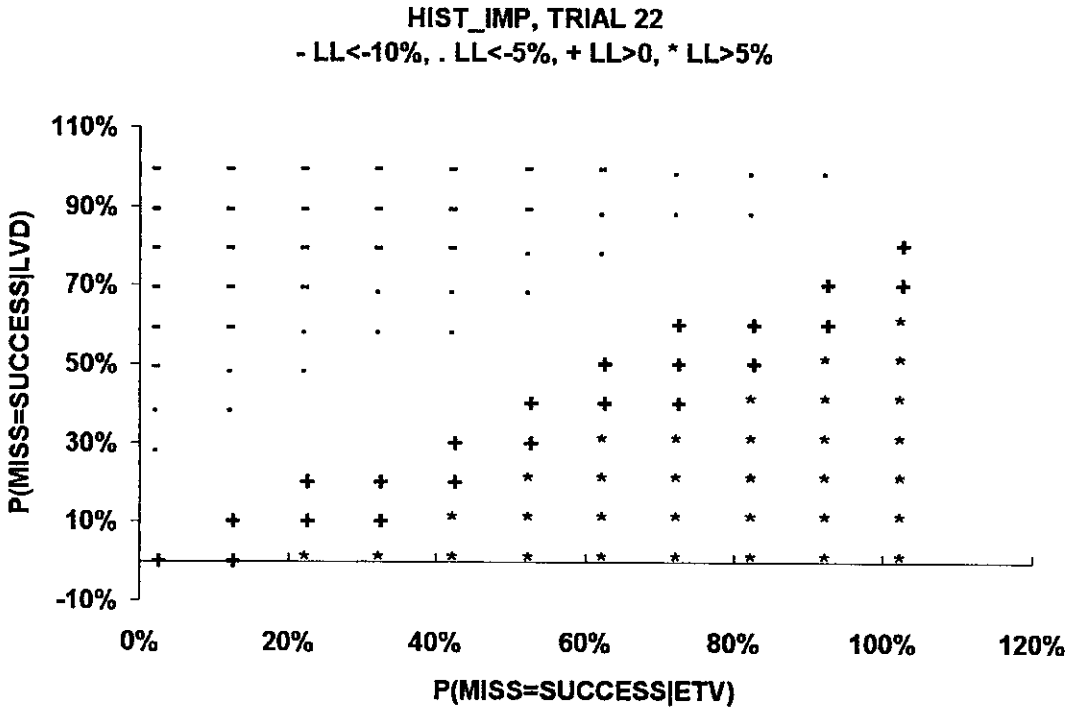
Figure 3.1.2 A plots the p-values for testing whether the rate of histological improvement is higher for ETV than for LVD in trial 26, assuming that anywhere from 0% to 100% of the missing data are successes. Stars indicate assumptions about success rates among the missing values that yield the conclusion that ETV is statistically significantly better than LVD with a one-sided p-value <.01; plus signs correspond to ETV is better than LVD with a one-sided p-value between .01 and .05; blanks correspond to ETV is better than LVD with a one-sided p-value between .05 and .1; periods correspond to ETV is better than LVD with a one-sided p-value between .1 and .5; minus signs correspond to LVD is better than ETV.

One can see that if one assumes that 40% or fewer of the missing LVD subjects were successes than the one-sided p-value in favor of ETV is always <.05 and usually <.01. In fact, one has to assume that the proportion of successes among missing values has to be at least 50-60% higher on LVD than on ETV in order to get one-sided p-values in favor of ETV to be >.1; one has to assume that the proportion of successes among missing values has to be at least 80% higher on LVD than on ETV in order to get an estimated LVD benefit > the estimated ETV benefit.

Because trials 22 and 27 were planned as non-inferiority trials in LVD naive subjects, the results of the sensitivity analyses on these two trials are given in terms of the two-sided 95% lower confidence bound for percent improved on ETV minus percent improved on LVD. The results for trial 22 are given in figure 3.1.2 B, those for trial 27 in figure 3.1.2 C.



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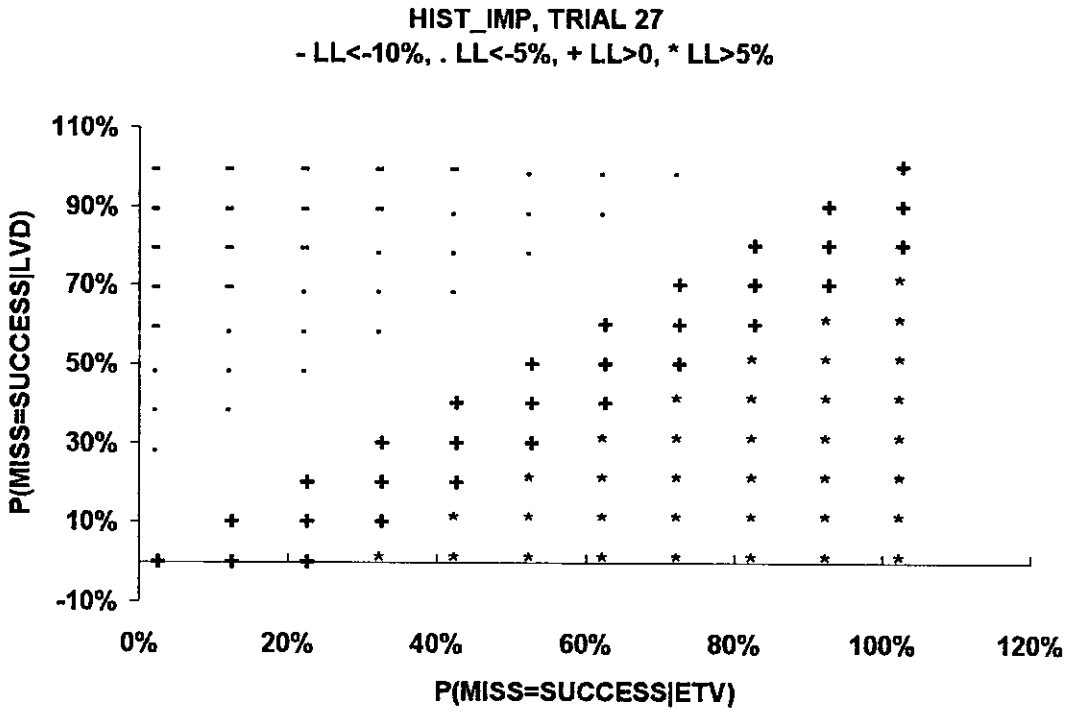
As with figure 3.1.2 A, results are coded so that stars, plus signs, blanks, periods, and minus signs show assumptions about success rates among the missing values that go from very favorable to ETV to very unfavorable to ETV. In these two plots, stars indicate assumptions that yield the conclusion that ETV is with two-sided 95% confidence at least 5% better than LVD; plus signs correspond to ETV is with 95% confidence at least as good as LVD; blanks correspond to ETV being no more than 5% worse than LVD; periods correspond to ETV being no more than 10% worse than LVD; minus signs correspond to being unable to conclude with 95% confidence that ETV is no more than 10% worse than LVD. Given that a delta of -10% constitutes support for a conclusion of non-inferiority, then only the region with minus signs corresponds to assumptions that lead to a conclusion of inferiority.

As with trial 26, one can see that one has to assume that success rate among missing values is 40-50% higher for LVD than for ETV in order to cast doubt on the conclusion of non-inferiority. In fact, if all missing data had been observed and the success rate among the missing values had been between 0% and 20% better on ETV (specifically, 0% on both arms, or 50% on ETV and 40% on LVD, or 100% on ETV and 80% on LVD), ETV would have been statistically significantly superior to LVD. One should recall that treating all missing values as failures leads to more data and narrower confidence limits than does discarding all missing values.



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Results in trial 27 are quite similar to those in trial 26. One has to assume that success rate among missing values is 50-60% higher for LVD than for ETV in order to cast doubt on the conclusion of non-inferiority. Again, if all missing data had been observed and the success rate among the missing values had been the same on both arms, ETV would have been statistically significantly superior to LVD.

3.1.2 Predictability of Biopsy from HBV DNA and ALT

There are two reasons for investigating whether biopsy results can be predicted from baseline and on treatment values of HBV DNA and ALT and from other baseline or on treatment covariates. First, if successful predictions can be made, one can perform sensitivity analyses in the current trial by imputing values to the subjects with missing biopsies using measured covariates. Second, it would contribute to selection of a surrogate marker for biopsy results in subsequent trials with ETV or other drugs.

The FDA reviewer estimated the probability of success on the histological improvement variable for trials 22, 26, and 27 by univariate and multivariate logistic regression (fitting a model in which log odds of success = a linear function of the predictor covariates). A prediction of success or failure was then made according to whether the estimated probability of success was >.5 or <.5. For comparison purposes, the reviewer also looked at the prediction made using no covariates. In this case, the prediction for every subject on a given treatment arm was the more common of the two possible outcomes for that treatment arm.

In table 3.1.2 A, the percent of predictions that agree with the observed outcome are tabled for trial 26 (LVD experienced subjects). The percent of correct predictions is given for all subjects in a given arm and for subjects predicted to be failures or predicted to be successes in that arm. The percents of correct predictions were computed using no predictors at all, using only baseline covariates, and using baseline plus on treatment covariates. The choices of covariates were selected

out of several candidate sets by methods not detailed here.

The baseline predictors were ALT, bDNA, AST, Age, sex, baseline PCR, creatinine, INR, BMI, blood pressure, weight, and previous interferon use. The on treatment predictors were ALT, HBV DNA, and HBE antibody level and HBE antigen level at weeks, all measured at weeks 12, 24, 36, and 48.

One can see that one can get 62% and 67% of the two arms correct without any predictors just predicting everyone in each arm to have the more likely outcome in that arm. (These percents agree with those in table 3.1.1 A, using method C.) Using only baseline covariates, one can improve the prediction rate to 64% and 77%; using baseline and on treatment covariates, one can get 74% and 91% correct.

TABLE 3.1.2 A
PERCENT CORRECT PREDICTIONS
OF HISTOLOGIC IMPROVEMENT, TRIAL_26

		Percent Correct			Number Correct		
			Predicted			Predicted	
PREDICTORS	TRT	All	Fail	Succ	All	Fail	Success
None	ETV	62%	.	62%	68	.	68
	LVD	67%	67%	.	66	66	.
Baseline	ETV	64%	59%	67%	59	17	42
	LVD	77%	80%	70%	64	48	16
Baseline + On_treatment	ETV	74%	73%	75%	67	24	43
	LVD	91%	92%	88%	69	47	22

In table 3.1.2 B, the percent of correct predictions are tabled for trials 22 and 27 (LVD naive subjects) pooled. The same predictors were used as in trial 26.

One can see that one can get 78% and 71% of the two arms correct without any predictors just predicting everyone in each arm to have the more likely outcome in that arm. Using only baseline covariates, one cannot improve the prediction rate for ETV but can improve the prediction rate for LVD to 73%; using baseline and on treatment covariates, one can get 79% and 76%

correct.

TABLE 3.1.2 B
PERCENT CORRECT PREDICTIONS
OF HISTOLOGIC IMPROVEMENT, TRIALS 22 & 27 POOLED

		Percent Correct Predicted			Number Correct Predicted		
PREDICTORS	TRT	All	Fail	Succ	All	Fail	Success
None	ETV	78%	.	78%	434	.	434
	LVD	71%	.	71%	369	.	369
Baseline	ETV	78%	.	78%	374	.	374
	LVD	73%	64%	74%	332	14	318
Baseline+ On_treatment	ETV	79%	65%	79%	350	11	339
	LVD	76%	68%	77%	316	34	282

The FDA reviewer then conducted a sensitivity analysis for the missing biopsy data by using the baseline and on-treatment predictors described above to impute a histologic improvement score for every subject with missing biopsy. (There may still missing scores for any subject without a complete set of predictors.) Table 3.1.2 C compares the percentages of subjects with histologic improvement in each arm, using both observed only and observed plus imputed data, for all three trials. It also gives the difference between ETV and LVD and 95% confidence limits for the difference.

TABLE 3.1.2 C
HISTOLOGIC IMPROVEMENT BY ARM AND TRIAL
OBSERVED OR IMPUTED DATA

	Mean Diff	95% Limits Lower	Upper	Ratios, Percents ETV	LVD	Pvalue
Trial_26						
Observed	29.2%	16.2%	42.2%	68/110=62%	32/98=33%	<.0001
Imputed	27.7%	16.8%	38.7%	78/141=55%	40/145=28%	<.0001
Trial_22						
Observed	4.9%	-2.3%	12.1%	226/292=77%	195/269=72%	.18
Imputed	9.2%	2.4%	16.0%	259/354=73%	227/355=64%	.008
Trial_27						
Observed	8.9%	1.3%	16.4%	208/265=78%	174/250=70%	.021
Imputed	10.2%	3.2%	17.3%	245/325=75%	204/313=65%	.0046

One can see that the most likely imputations of missing biopsy data make no practical difference in trials 26 and 27. In trial 22, the imputation suggests that the true difference between ETV and LVD may have been more favorable to ETV than the observed data.

The second reason for exploring imputations of missing biopsy data was to explore potential surrogate markers for biopsy data in future trials. Although, one might expect that predictions would be more accurate if separate models were used for each arm, this is undesirable for selection of a surrogate marker for biopsy because treatment arm is itself a potential predictor of histological success. (This is certainly the case for the LVD experienced subjects.) Using treatment as one of the

predictors will thus be potentially misleading about the value of the other variables as surrogate markers in future trials.

In table 3.1.2 D, the percent of predictions that agree with the observed outcome are tabled for trial 26 (LVD experienced subjects). The percent of correct predictions is given for all subjects in a given arm and for subjects predicted to be failures or predicted to be successes in that arm. The percents of correct predictions were computed using no predictors at all, using only a short list of baseline predictors (ALT, HBV DNA, AST, and age), and using the baseline list plus four possible on-treatment lists: ALT and HBV DNA measured 1) only at week 12, 2) at weeks 12 and 24, 3) at weeks 12, 24, and 36, and 4) at weeks 12, 24, 36, and 48. Further explorations suggested that adding E antibody and E antigen level added minimally to the accuracy of predictions. (A full list of the candidate sets of predictors explored is given in the appendix.)

TABLE 3.1.2 D
PERCENT CORRECT PREDICTIONS
OF HISTOLOGIC IMPROVEMENT,

TRIAL_26	Percent Correct			Number Correct		
		Predicted			Predicted	
Predictors	All	Fail	Succ	All	Fail	Success
None	52%	52%	.	108	108	.
Baseline	59%	59%	58%	122	71	51
Base+Week_12	68%	69%	67%	140	74	66
Base+Weeks_12-24	68%	68%	67%	137	75	62
Base+Weeks_12-36	70%	71%	68%	139	74	65
Base+Weeks_12-48	70%	73%	67%	137	69	68
TRIALS_22_&_27_POOLED						
None	75%	.	75%	803	.	803
Baseline	75%	.	75%	798	.	798
Base+Week_12	75%	100%	75%	794	2	792
Base+Weeks_12-24	75%	67%	75%	774	6	768
Base+Weeks_12-36	76%	68%	76%	741	19	722
Base+Weeks_12-48	76%	63%	76%	740	26	714

One will notice that in trial 26, where the success rate was only about 50%, significant increases in accuracy can be made by adding baseline and on-treatment measurements to the list of predictors. In trials 22 and 27, where the success rate was 75%, no real increase in accuracy can be obtained by using potential predictors.

One might conjecture that the lack of improvement in predictability is due to the predictability has been lost because an ordinal variable, Knodell score, has been compressed into a binary variable, histological improvement. To explore this possibility, one can look at table 3.1.2 E, which shows the adjusted square correlation (adjusted downward for the number of predictors used) for change in Knodell necrosis score predicted by linear regression on baseline and on treatment predictors. One additional exploratory result, using a long list of baseline predictors (=short baseline list plus sex, weight, prior interferon use, E antibody and antigen levels, creatinine, albumen, total bilirubin, and blood pressure) is included.

TABLE 3.1.2 E
ADJUSTED SQUARE CORRELATIONS
OF KNODELL NECROSIS SCORE

	Adjusted R^2	
Predictors	Trial_26	Trials_22_&_27
Short Baseline	.030	.066
Long Baseline	.049	.069
Short Base+Week_12	.147	.072
Short Base+Weeks_12-24	.127	.086
Short Base+Weeks_12-36	.134	.112
Short Base+Weeks_12-48	.163	.150

One can notice two things from this table. First, adding progressively more on treatment covariates does improve predictability of biopsy results slightly. The percent of variation explained increased from 3-7% to 16-15%. The other fact is that predictability, even with the complete course of on treatment covariates used still produces only a slight reduction (15-16%) in the residual variability of Knodell necrosis score. Adding in more baseline covariates along with the on treatment covariates actually reduces predictability because of the

adjustment for number of predictors and because of missing values among the predictors.

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The four sets of baseline predictors were 1) a short baseline list (ALT, bDNA, AST, and Age), 2) a middle baseline list (the short list plus sex, baseline PCR, creatinine, INR, BMI, blood pressure, weight, and previous interferon use), 3) a moderate baseline list (the middle list plus albumen, total bilirubin, and prothrombin time), and 4) a long baseline list (the moderate list plus HBE antibody level and HBE antigen level).

The three sets of on-treatment predictors were 1) a short list (= ALT and HBV DNA measured by one assay at weeks 12, 24, 36, and 48), 2) a middle list (= short list plus HBV DNA measured by both assays), and 3) a long list (=middle list + HBE antibody level and HBE antigen level at weeks 12, 24, 36, and 48).

The set of candidate predictors was obtained from a larger list of all available predictors by selecting those predictors with the highest univariate correlations and then discarding those predictors with low correlation in the largest multivariate model. The results from those preliminary analyses are not given here nor are the full set of all 13 examined multivariate regression.

One can see that one can get 62% and 67% of the two arms correct without any predictors just predicting everyone in each arm to have the more likely outcome in that arm. (These percents agree with those in table 3.1.1 A, using method C.) Using only baseline covariates, one can improve the prediction rate to 64% and 77%; using baseline and on treatment covariates, one can get 73% and 91% correct.

TABLE 3.1.2 A
PERCENT CORRECT PREDICTIONS
OF HISTOLOGIC IMPROVEMENT, TRIAL_26

		Percent Correct Among Predicted		
PREDICTORS	TRT	All	Fail	Success
None	ETV	62%	.	62%
	LVD	67%	67%	.
Middle_base	ETV	64%	59%	67%
	LVD	77%	80%	70%
Middle_base+ middle_on_trt	ETV	73%	68%	76%
	LVD	91%	92%	88%

In table 3.1.2 B, the percent of correct predictions are tabled for trials 22 and 27 (LVD naive subjects) pooled. The percents of correct predictions are given for the most promising of the thirteen sets of multivariate predictors examined.

One can see that one can get 78% and 71% of the two arms correct without any predictors just predicting everyone in each arm to have the more likely outcome in that arm. Using only baseline covariates, one cannot improve the prediction rate for ETV but can improve the prediction rate for LVD to 73%; using baseline and on treatment covariates, one can get 79% and 76% correct.

TABLE 3.1.2 B

PERCENT CORRECT PREDICTIONS

OF HISTOLOGIC IMPROVEMENT, TRIALS 22 & 27 POOLED

		Percent Correct Among Predicted		
PREDICTORS	TRT	All	Fail	Success
None	ETV	78%	.	78%
	LVD	71%	.	71%
Middle_base	ETV	78%	.	78%
	LVD	73%	64%	74%
Middle_base+ Long_on_trt	ETV	79%	65%	79%
	LVD	76%	68%	77%

3.1.3 Sensitivity Analyses on HBV DNA and ALT Results

Results in which subjects who are missing end week (24 or 48) datum are discarded. Results compare each ETV arm (arm 1) to LVD (arm 2). In trial 14, there are 3 results for the three ETV doses. Results are presented as ETV-LVD, lower and upper 95% limits for the difference, ETV # successful, # at risk, % successful, LVD # successful, # at risk, % successful,

TABLE 3.1.3 A
NORMAL ALT

ENDPT	MEAN DIFF	95% LIMITS LOWER	UPPER	# Succ/# Arm = % Success ETV	LVD	PVALUE
TRIAL 14_ETV_1.0						
<1.25				22/42=52%	19/45=42%	.12
<1	15.0%	-6.0%	35.0%	17/40=43%	12/43=28%	.16
TRIAL 26						
<1.25	52%	42%,	62%	106/141=75%	34/145=23%	<.0001
<1	48.0%	38.0%	59.0%	87/134=65%	22/132=17%	<.0001
TRIAL 22						
<1.25	8.1%	1.7%,	14.5%	277/354=78%	249/355=70%	.0136
<1	5.0%	-2.0%	12.0%	243/342=71%	215/324=66%	.19
TRIAL 27						
<1.25	4.1%	-1.7%,	9.8%	278/325=86%	255/313=81%	.17
<1	7.0%	.0%	13.0%	255/316=81%	222/300=74%	.047

Table 3.1.3 B compares the percentages BLQ for HBV DNA by the bDNA and PCR assays by two methods. The first uses the applicant's method of counting all subjects randomized as failures if the week 48 result (week 24 in trial 14) is missing; the second only uses subjects who actually have the final HBV DNA measurement. One can see that this makes little difference in the conclusions.

TABLE 3.1.3 B
HBV DNA BLQ

ENDPT	MEAN DIFF	95% LIMITS LOWER	UPPER	# Succ/# Arm = % Success ETV	LVD	PVALUE
TRIAL 14						
bDNA	65%	40%,	91%	33/42=79%	6/45=13%	<.0001
PCR	14.4%	2.3%,	26.6%	7/42=17%	1/45=2%	.0198
bDNA	69.0%	53.0%	84.0%	33/40=83%	6/43=14%	<.0001
PCR	15.0%	3.0%,	28.0%	7/40=18%	1/43=2%	.0183
TRIAL 26						
bDNA	60%	52%,	69%	93/141=66%	8/145=6%	<.0001
PCR	19.2%	12.3%,	26.1%	29/141=21%	2/145=1%	<.0001
bDNA	65.0%	57.0%,	74.0%	94/134=70%	6/129=5%	<.0001
PCR	21.0%	14.0%,	28.0%	29/134=22%	1/129=1%	<.0001
TRIAL 22						
bDNA	26%	20%,	31%	322/354=91%	232/355=65%	<.0001
PCR	32%	25%,	38%	246/354=69%	135/355=38%	<.0001
bDNA	22.0%	17.0%	27.0%	324/341=95%	235/322=73%	<.0001
PCR	30.0%	23.0%,	38.0%	246/341=72%	135/323=42%	<.0001
TRIAL 27						
bDNA	5.9%	1.8%,	10.1%	309/325=95%	279/313=89%	.0053
PCR	18%	12%,	24%	297/325=91%	230/313=73%	<.0001
bDNA	5.0%	2.0%,	8.0%	309/311=99%	280/297=94%	.0004
PCR	18.0%	12.0%,	23.0%	295/312=95%	228/296=77%	<.0001

There were a few discrepancies between the number of successes counted by the applicant and by the FDA reviewer. These are inconsequential in number and mostly due to the FDA reviewer counting a subject as missing if his HBV DNA measurement in the week 48 window occurred more than 10 days after stopping the assigned treatment. Also the sponsor appears to have interpolated missing week 48 data from previous and subsequent visits while the FDA reviewer treated such subjects as missing in the sensitivity analyses.

3.2 Evaluation of Safety

There were no statistically apparent safety concerns with this NDA. Safety raised by non-statistically significant but subjectively interesting patterns are addressed in the clinical reviews.

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4. Results in Special Populations

4.1 Gender, Race, and Age

The following tables (4.1 A-I) give the results on percent improved with respect to a) primary histologic criterion, b) Knodell fibrosis score or c) Knodell necrosis score. Missing subjects are discarded from numerator and denominator. The counts and percents in the ETV and LVD arms are given together with the difference between ETV and LVD and the 95% upper and lower limits for the difference.

Results are stratified by sex, race, and quartile of age. In section 4.2, the results on overall improvement are given stratified by HBeAb, HBeAg, and HBsAg status, subtype, quartiles of log baseline HBV DNA by bDNA assay, of log baseline HBV DNA by PCR assay, prior interferon use, prior LVD use, quartiles of baseline ALT, baseline ALT status, baseline ALT toxicity grade by WHO standards, quartiles of baseline AST, of international normalized ratio, of prothrombin time, of total bilirubin, of baseline creatinine, of baseline diastolic blood pressure, of baseline systolic blood pressure, country, and region. Anything ending in _Q is a continuous covariate divided into quartiles.

TABLE 4.1 A
WEEK 48 HISTOLOGIC IMPROVEMENT
TRIAL 26

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
Pooled	26.0%	16.0%	37.0%	68/141=48%	32/145=22%
SEX					
Female	14.0%	-9.0%	37.0%	17/36=47%	11/33=33%
Male	30.0%	18.0%	42.0%	51/105=49%	21/112=19%
RACE_					
Asian	31.0%	14.0%	48.0%	29/58=50%	10/52=19%
White	23.0%	10.0%	37.0%	39/83=47%	22/93=24%
AGE_Q					
<=27	23.0%	2.0%	44.0%	22/43=51%	10/36=28%
27-38	43.0%	22.0%	65.0%	18/30=60%	6/36=17%
38-49	11.0%	-11.0%	32.0%	12/33=36%	10/39=26%
>49	28.0%	7.0%	49.0%	16/35=46%	6/34=18%

TABLE 4.1 B
WEEK 48 KNODELL FIBROSIS IMPROVEMENT
TRIAL 26

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
Pooled	14.0%	6.0%	21.0%	28/141=20%	9/145=6%
SEX					
Female	17.0%	4.0%	29.0%	6/36=17%	0/33=0%
Male	13.0%	4.0%	22.0%	22/105=21%	9/112=8%
RACE_					
Asian	20.0%	8.0%	32.0%	14/58=24%	2/52=4%
White	9.0%	0.0%	19.0%	14/83=17%	7/93=8%
AGE_Q					
<=27	8.0%	-4.0%	21.0%	6/43=14%	2/36=6%
27-38	18.0%	0.0%	37.0%	8/30=27%	3/36=8%
38-49	22.0%	6.0%	37.0%	8/33=24%	1/39=3%
>49	8.0%	-7.0%	24.0%	6/35=17%	3/34=9%

TABLE 4.1 C
WEEK 48 KNODELL NECROSIS IMPROVEMENT
TRIAL 26

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
Pooled	23.0%	12.0%	34.0%	68/141=48%	37/145=26%
SEX					
Female	8.0%	-15.0%	31.0%	17/36=47%	13/33=39%
Male	27.0%	15.0%	39.0%	51/105=49%	24/112=21%
RACE_					
Asian	29.0%	12.0%	46.0%	29/58=50%	11/52=21%
White	19.0%	5.0%	33.0%	39/83=47%	26/93=28%
AGE_Q					
<=27	21.0%	-1.0%	42.0%	22/43=51%	11/36=31%
27-38	43.0%	22.0%	65.0%	18/30=60%	6/36=17%
38-49	8.0%	-13.0%	30.0%	12/33=36%	11/39=28%
>49	19.0%	-3.0%	41.0%	16/35=46%	9/34=26%

TABLE 4.1 D
WEEK 48 HISTOLOGIC IMPROVEMENT
TRIAL 22

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
Pooled	9.0%	2.0%	16.0%	226/354=64%	195/355=55%
SEX					
Female	11.0%	-4.0%	25.0%	51/80=64%	50/94=53%
Male	8.0%	0.0%	17.0%	175/274=64%	145/261=56%
RACE_					
Asian	7.0%	-3.0%	16.0%	130/204=64%	116/204=57%
Black	4.0%	-41.0%	50.0%	6/9=67%	5/8=63%
Other	0.0%	0.0%	0.0%	1/1=100%	2/2=100%
White	13.0%	1.0%	24.0%	89/140=64%	72/141=51%
AGE_Q					
<=24	14.0%	0.0%	28.0%	59/91=65%	46/91=51%
24-32	3.0%	-11.0%	18.0%	52/85=61%	51/88=58%
32-43	5.0%	-9.0%	19.0%	57/94=61%	49/88=56%
>43	13.0%	-1.0%	28.0%	58/84=69%	49/88=56%

TABLE 4.1 E
WEEK 48 KNODELL FIBROSIS IMPROVEMENT
TRIAL 22

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
Pooled	1.0%	-4.0%	7.0%	61/354=17%	57/355=16%
SEX					
Female	8.0%	-2.0%	19.0%	15/80=19%	10/94=11%
Male	-1.0%	-8.0%	5.0%	46/274=17%	47/261=18%
RACE_					
Asian	2.0%	-5.0%	9.0%	37/204=18%	33/204=16%
Black	-15.0%	-58.0%	28.0%	2/9=22%	3/8=38%
Other	0.0%	0.0%	0.0%	0/1=0%	0/2=0%
White	1.0%	-8.0%	9.0%	22/140=16%	21/141=15%
AGE_Q					
<=24	5.0%	-4.0%	15.0%	14/91=15%	9/91=10%
24-32	2.0%	-10.0%	13.0%	16/85=19%	15/88=17%
32-43	-3.0%	-14.0%	7.0%	13/94=14%	15/88=17%
>43	1.0%	-11.0%	13.0%	18/84=21%	18/88=20%

TABLE 4.1 F
WEEK 48 KNODELL NECROSIS IMPROVEMENT
TRIAL 22

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
Pooled	9.0%	2.0%	16.0%	231/354=65%	200/355=56%
SEX					
Female	12.0%	-3.0%	26.0%	52/80=65%	50/94=53%
Male	8.0%	0.0%	16.0%	179/274=65%	150/261=57%
RACE_					
Asian	5.0%	-4.0%	15.0%	130/204=64%	119/204=58%
Black	4.0%	-41.0%	50.0%	6/9=67%	5/8=63%
Other	0.0%	0.0%	0.0%	1/1=100%	2/2=100%
White	15.0%	3.0%	26.0%	94/140=67%	74/141=52%
AGE_Q					
<=24	14.0%	0.0%	28.0%	59/91=65%	46/91=51%
24-32	1.0%	-14.0%	16.0%	52/85=61%	53/88=60%
32-43	5.0%	-9.0%	19.0%	59/94=63%	51/88=58%
>43	16.0%	2.0%	30.0%	61/84=73%	50/88=57%

TABLE 4.1 G
WEEK 48 HISTOLOGIC IMPROVEMENT
TRIAL 27

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
Pooled	8.0%	1.0%	16.0%	208/325=64%	174/313=56%
SEX					
Female	0.0%	-15.0%	15.0%	46/77=60%	46/77=60%
Male	11.0%	2.0%	20.0%	162/248=65%	128/236=54%
RACE_					
Asian	5.0%	-7.0%	17.0%	80/123=65%	77/129=60%
Black	32.0%	-15.0%	80.0%	6/8=75%	3/7=43%
White	10.0%	0.0%	20.0%	122/194=63%	94/177=53%
AGE_Q					
<=37	0.0%	-15.0%	14.0%	54/85=64%	51/80=64%
37-45	8.0%	-7.0%	22.0%	57/85=67%	51/86=59%
45-53	9.0%	-6.0%	25.0%	51/80=64%	44/81=54%
>53	19.0%	3.0%	35.0%	46/75=61%	28/66=42%

TABLE 4.1 H
WEEK 48 KNODELL FIBROSIS IMPROVEMENT
TRIAL 27

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
Pooled	-3.0%	-9.0%	3.0%	54/325=17%	62/313=20%
SEX					
Female	-1.0%	-13.0%	10.0%	12/77=16%	13/77=17%
Male	-4.0%	-11.0%	3.0%	42/248=17%	49/236=21%
RACE_					
Asian	-10.0%	-20.0%	-1.0%	16/123=13%	30/129=23%
Black	-4.0%	-49.0%	41.0%	2/8=25%	2/7=29%
White	2.0%	-6.0%	9.0%	36/194=19%	30/177=17%
AGE_Q					
<=37	-12.0%	-24.0%	0.0%	11/85=13%	20/80=25%
37-45	4.0%	-7.0%	14.0%	14/85=16%	11/86=13%
45-53	-5.0%	-17.0%	8.0%	14/80=18%	18/81=22%
>53	0.0%	-13.0%	13.0%	15/75=20%	13/66=20%

TABLE 4.1 I
WEEK 48 KNODELL NECROSIS IMPROVEMENT
TRIAL 27

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
Pooled	8.0%	1.0%	16.0%	217/325=67%	183/313=58%
SEX					
Female	-4.0%	-19.0%	11.0%	47/77=61%	50/77=65%
Male	12.0%	4.0%	21.0%	170/248=69%	133/236=56%
RACE_					
Asian	7.0%	-5.0%	19.0%	85/123=69%	80/129=62%
Black	32.0%	-15.0%	80.0%	6/8=75%	3/7=43%
White	8.0%	-1.0%	18.0%	126/194=65%	100/177=56%
AGE_Q					
<=37	0.0%	-15.0%	14.0%	55/85=65%	52/80=65%
37-45	7.0%	-8.0%	21.0%	59/85=69%	54/86=63%
45-53	11.0%	-4.0%	26.0%	54/80=68%	46/81=57%
>53	18.0%	2.0%	35.0%	49/75=65%	31/66=47%

The following tables (tables 4.1 J-O) give the results on percent with a) final ALT < ULN (not < 1.25ULN) or b) HBV DNA BLQ on PCR assay in trials 14, 26, and 22-27 pooled. For trial 14, only results from the ETV 1 mg arm are given. Missing subjects are counted as failures. Note that this is different from the handling of histologic variables.

The counts and percents in the ETV and LVD arms are given together with the difference between ETV and LVD and the 95% upper and lower limits for the difference. Results are stratified by sex, race, and quartile of age.

TABLE 4.1 J
WEEK 24 ALT < ULN
TRIAL 14

Covariate	Diff	95% Limit Lower	Upper	Mean Change ETV/r	LVD
	14.0%	-6.0%	33.0%	17/42=40%	12/45=27%
SEX					
Female	39.0%	-20.0%	99.0%	2/3=67%	3/11=27%
Male	12.0%	-9.0%	33.0%	15/39=38%	9/34=26%
RACE					
Asian	23.0%	-13.0%	58.0%	9/13=69%	7/15=47%
White	10.0%	-11.0%	32.0%	7/26=27%	5/30=17%
AGE_Q					
<=37	27.0%	-12.0%	67.0%	8/11=73%	5/11=45%
37-45	32.0%	-8.0%	72.0%	4/9=44%	1/8=13%
45-57	25.0%	-10.0%	60.0%	5/12=42%	2/12=17%
>57	-29.0%	-52.0%	-5.0%	0/10=0%	4/14=29%

TABLE 4.1 K
WEEK 24 HBV PCR < 1000
TRIAL 14

Covariate	Diff	95% Limit Lower	Upper	Mean Change ETV/r	LVD
	19.0%	6.0%,	32.0%	9/42=21%	1/45=2%
SEX					
Female	0.0%	0.0%,	0.0%	0/3=0%	0/11=0%
Male	20.0%	6.0%,	35.0%	9/39=23%	1/34=3%
RACE					
Asian	15.0%	-4.0%,	35.0%	2/13=15%	0/15=0%
White	20.0%	2.0%,	37.0%	6/26=23%	1/30=3%
AGE_Q					
<=37	27.0%	1.0%,	54.0%	3/11=27%	0/11=0%
37-45	11.0%	-9.0%,	32.0%	1/9=11%	0/8=0%
45-57	33.0%	7.0%,	60.0%	4/12=33%	0/12=0%
>57	3.0%	-20.0%,	26.0%	1/10=10%	1/14=7%

TABLE 4.1 L
WEEK 48 ALT < ULN
TRIAL 26

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
	47.0%	37.0%	56.0%	87/141=62%	22/145=15%
SEX					
Female	51.0%	31.0%	71.0%	25/36=69%	6/33=18%
Male	45.0%	33.0%	56.0%	62/105=59%	16/112=14%
RACE_					
Asian	56.0%	42.0%	70.0%	37/58=64%	4/52=8%
White	41.0%	28.0%	54.0%	50/83=60%	18/93=19%
AGE_Q					
<=27	39.0%	19.0%	58.0%	25/43=58%	7/36=19%
27-38	58.0%	39.0%	77.0%	19/30=63%	2/36=6%
38-49	42.0%	22.0%	63.0%	19/33=58%	6/39=15%
>49	48.0%	27.0%	69.0%	24/35=69%	7/34=21%

TABLE 4.1 M
WEEK 48 HBV PCR < 1000
TRIAL 26

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
	25.0%	18.0%,	32.0%	36/141=26%	1/145=1%
SEX					
Female	17.0%	4.0%,	29.0%	6/36=17%	0/33=0%
Male	28.0%	19.0%,	36.0%	30/105=29%	1/112=1%
RACE_					
Asian	28.0%	16.0%,	39.0%	16/58=28%	0/52=0%
White	23.0%	14.0%,	32.0%	20/83=24%	1/93=1%
AGE_Q					
<=27	18.0%	5.0%,	31.0%	9/43=21%	1/36=3%
27-38	27.0%	11.0%,	42.0%	8/30=27%	0/36=0%
38-49	24.0%	10.0%,	39.0%	8/33=24%	0/39=0%
>49	31.0%	16.0%,	47.0%	11/35=31%	0/34=0%

TABLE 4.1 N
WEEK 48 ALT < ULN
TRIALS 22 & 27 POOLED

Covariate	Diff	95% Limit Lower	Upper	Mean Change ETV/r	LVD
	8.0%	3.0%,	13.0%	499/679=73%	438/668=66%
SEX					
Female	7.0%	-3.0%,	16.0%	125/157=80%	125/171=73%
Male	9.0%	3.0%,	14.0%	374/522=72%	313/497=63%
RACE_					
Asian	6.0%	-1.0%,	13.0%	233/327=71%	218/333=65%
Black	3.0%	-27.0%,	33.0%	13/17=76%	11/15=73%
Other	0.0%	0.0%,	0.0%	1/1=100%	2/2=100%
White	10.0%	3.0%,	17.0%	252/334=75%	207/318=65%
AGE_Q					
<=24	7.0%	-2.0%,	17.0%	131/176=74%	115/171=67%
24-32	9.0%	0.0%,	19.0%	130/170=76%	117/174=67%
32-43	3.0%	-6.0%,	13.0%	125/174=72%	116/169=69%
>43	13.0%	2.0%,	23.0%	113/159=71%	90/154=58%

TABLE 4.1 O
WEEK 48 HBV PCR < 1000
TRIALS 22 & 27 POOLED

Covariate	Diff	95% Limit Lower	Upper	Mean Change ETV/r	LVD
	26.0%	22.0%,	31.0%	576/679=85%	391/668=59%
SEX					
Female	25.0%	15.0%,	34.0%	135/157=86%	105/171=61%
Male	27.0%	22.0%,	32.0%	441/522=84%	286/497=58%
RACE_					
Asian	25.0%	19.0%,	32.0%	281/327=86%	202/333=61%
Black	15.0%	-12.0%,	42.0%	15/17=88%	11/15=73%
Other	50.0%	-19.0%,	100%	1/1=100%	1/2=50%
White	28.0%	21.0%,	35.0%	279/334=84%	177/318=56%
AGE_Q					
<=24	26.0%	16.0%,	35.0%	138/176=78%	90/171=53%
24-32	27.0%	19.0%,	36.0%	154/170=91%	110/174=63%
32-43	24.0%	15.0%,	33.0%	148/174=85%	103/169=61%
>43	28.0%	19.0%,	38.0%	136/159=86%	88/154=57%

4.2 Other Covariates

The following tables (4.2 B-D) give the results on percent with histological improvement in trials 26, 22, and 27. Missing subjects are discarded from numerator and denominator. The counts and percents in the ETV and LVD arms are given together with the difference between ETV and LVD and the 95% upper and lower limits for the difference.

Results are stratified by HBeAb, HBeAg, and HBsAg status, subtype, quartiles of log baseline HBV DNA by bDNA assay, of log baseline HBV DNA by PCR assay, prior interferon use, prior LVD use, quartiles of baseline ALT, baseline ALT status, baseline ALT toxicity grade by WHO standards, quartiles of baseline AST, of international normalized ratio, of prothrombin time, of total bilirubin, of baseline creatinine, of baseline diastolic blood pressure, of baseline systolic blood pressure, country, and region. Anything ending in _Q is a continuous covariate divided into quartiles.

The FDA reviewer performed Mantel-Haenszel tests for heterogeneity across subgroups (i.e., treatment-covariate interaction) for all the covariates in sections 4.1 and 4.2 for the histological improvement. The p-values for the 73 tests performed in trials 22, 26, and 27 are given in table 4.2 A, grouped by intervals of width .05. The number of expected p-values in any of the 20 intervals of width .05 was 3.65 if none of the 73 covariates had true heterogeneity in treatment effect. One can see that the p-values are distributed the way one would expect in the absence of any heterogeneity (treatment-covariate interaction).

TABLE 4.2 A

P-VALUES FOR HETEROGENEITY ACROSS SUBGROUPS

Range of p-value	0-.05	.05-.10	.10-.15	.15-.20	.20-.25	.25-.30
No. Observed p's	4	2	7	5	4	2

Range	.30-.35	.35-.40	.40-.45	.45-.50	.50-.55	.55-.60	.60-.65
Observed	5	3	3	3	4	3	3

Range	.65-.70	.70-.75	.75-.80	.80-.85	.85-.90	.90-.95	.95-1
Observed	3	6	4	2	6	2	2

TABLE 4.2 B
WEEK 48 HISTOLOGIC IMPROVEMENT
TRIAL 26

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
HBEAB					
Negative	25.0%	14.0%	35.0%	64/135=47%	32/140=23%
Positive	67.0%	29.0%	100%	4/6=67%	0/5=0%
HBEAG					
Negative	60.0%	17.0%	100%	3/5=60%	0/3=0%
Positive	25.0%	14.0%	36.0%	65/136=48%	32/142=23%
HBSAG					
Positive	26.0%	16.0%	37.0%	68/141=48%	32/145=22%
SUBTYPE					
AG	0.0%	0.0%	0.0%	0/1=0%	0/3=0%
D	9.0%	-9.0%	28.0%	17/45=38%	16/56=29%
Indeter.	17.0%	-71.0%	100%	1/2=50%	1/3=33%
B	26.0%	-5.0%	56.0%	14/23=61%	6/17=35%
A	27.0%	5.0%	48.0%	18/37=49%	7/32=22%
C	45.0%	24.0%	66.0%	14/27=52%	2/28=7%
F	75.0%	33.0%	100%	3/4=75%	0/3=0%
	100%	100%	100%	1/1=100%	0/2=0%
LBASEB_Q					
<=2.18	34.0%	12.0%	56.0%	19/33=58%	9/38=24%
2.18-2.66	15.0%	-7.0%	37.0%	17/38=45%	10/34=29%
2.66-3.08	31.0%	10.0%	52.0%	18/37=49%	6/34=18%
>3.08	24.0%	4.0%	45.0%	14/33=42%	7/39=18%
LBASEP_Q					
<=8.51	23.0%	1.0%	45.0%	17/33=52%	11/39=28%
8.51-9.29	36.0%	15.0%	57.0%	21/36=58%	8/36=22%
9.29-9.91	9.0%	-12.0%	30.0%	11/33=33%	9/37=24%
>9.91	37.0%	17.0%	56.0%	19/39=49%	4/33=12%
PRIORINT					
N	27.0%	12.0%	42.0%	33/71=46%	13/67=19%
Y	26.0%	11.0%	41.0%	35/70=50%	19/78=24%
PRIORLVD					
Y	26.0%	15.0%	37.0%	68/141=48%	32/144=22%

TABLE 4.2 B (cont.)
WEEK 48 HISTOLOGIC IMPROVEMENT
TRIAL 26

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
BLALT_Q					
<=59	23.0%	2.0%	43.0%	17/38=45%	8/36=22%
59-86	9.0%	-12.0%	29.0%	9/30=30%	9/42=21%
86-131	31.0%	9.0%	52.0%	17/34=50%	7/36=19%
>131	38.0%	17.0%	60.0%	25/39=64%	8/31=26%
ALTSTS_					
<1.25*ULN	12.0%	-16.0%	40.0%	10/24=42%	6/20=30%
>=1.25*ULN	29.0%	17.0%	40.0%	58/117=50%	26/124=21%
ALTWHO					
0	12.0%	-16.0%	40.0%	10/24=42%	6/20=30%
1	21.0%	6.0%	36.0%	28/66=42%	18/84=21%
2	35.0%	11.0%	58.0%	17/31=55%	5/25=20%
3	34.0%	-4.0%	72.0%	10/17=59%	2/8=25%
4	86.0%	60.0%	100%	3/3=100%	1/7=14%
AST_Q					
<=38	24.0%	3.0%	44.0%	13/32=41%	7/41=17%
38-50	18.0%	-4.0%	40.0%	15/32=47%	12/42=29%
50-74	17.0%	-3.0%	38.0%	14/38=37%	6/31=19%
>74	44.0%	23.0%	65.0%	26/39=67%	7/31=23%
INR_Q					
<=1.00	29.0%	14.0%	44.0%	38/72=53%	18/76=24%
1.00-1.03	31.0%	-14.0%	77.0%	6/10=60%	2/7=29%
1.03-1.11	21.0%	-2.0%	44.0%	13/30=43%	7/31=23%
>1.11	22.0%	0.0%	44.0%	11/29=38%	5/31=16%
PT_Q					
<=11.7	24.0%	5.0%	44.0%	21/43=49%	11/45=24%
11.7-12.6	14.0%	-9.0%	38.0%	16/31=52%	13/35=37%
12.6-14.0	44.0%	25.0%	62.0%	20/39=51%	2/27=7%
>14.0	23.0%	2.0%	45.0%	11/28=39%	6/38=16%
TBILI_Q					
<=0.6	29.0%	12.0%	46.0%	24/53=45%	8/49=16%
0.6-0.8	23.0%	2.0%	43.0%	19/40=48%	11/44=25%
0.8-1.0	30.0%	3.0%	57.0%	11/20=55%	7/28=25%
>1.0	25.0%	0.0%	50.0%	14/28=50%	6/24=25%

TABLE 4.2 B (cont.)
WEEK 48 HISTOLOGIC IMPROVEMENT
TRIAL 26

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
CREAT_Q					
<=0.8	23.0%	6.0%	41.0%	28/61=46%	11/49=22%
0.8-0.9	23.0%	4.0%	43.0%	12/33=36%	5/38=13%
0.9-1.0	38.0%	11.0%	66.0%	12/20=60%	5/23=22%
>1.0	28.0%	4.0%	52.0%	16/27=59%	11/35=31%
BMI_Q					
<=21.9	41.0%	21.0%	61.0%	24/39=62%	8/39=21%
21.9-24.1	21.0%	0.0%	43.0%	16/37=43%	7/32=22%
24.1-26.8	23.0%	2.0%	44.0%	12/31=39%	6/38=16%
>26.8	17.0%	-6.0%	39.0%	16/34=47%	11/36=31%
HT_Q					
<=165	22.0%	1.0%	42.0%	22/43=51%	12/41=29%
165-171	25.0%	3.0%	46.0%	16/35=46%	7/33=21%
171-176	23.0%	3.0%	44.0%	12/32=38%	5/35=14%
>176	36.0%	14.0%	58.0%	18/31=58%	8/36=22%
WT_Q					
<=62	31.0%	9.0%	52.0%	22/39=56%	9/35=26%
62-71	28.0%	8.0%	49.0%	17/36=47%	7/37=19%
71-80	24.0%	2.0%	45.0%	17/36=47%	8/34=24%
>80	19.0%	-2.0%	41.0%	12/30=40%	8/39=21%
BPDIA_Q					
<=70	30.0%	13.0%	47.0%	29/57=51%	11/53=21%
70-80	28.0%	11.0%	46.0%	28/55=51%	13/58=22%
>80	14.0%	-8.0%	37.0%	11/29=38%	8/34=24%
BPSYS_Q					
<=110	26.0%	8.0%	44.0%	25/52=48%	11/50=22%
110-120	28.0%	6.0%	51.0%	20/38=53%	7/29=24%
120-130	30.0%	7.0%	52.0%	12/26=46%	6/37=16%
>130	16.0%	-9.0%	42.0%	11/25=44%	8/29=28%

TABLE 4.2 B (cont.)
WEEK 48 HISTOLOGIC IMPROVEMENT
TRIAL 26

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
CNTRY					
Russia	0.0%	0.0%	0.0%	0/2=0%	0/4=0%
Turkey	9.0%	-14.0%	32.0%	13/32=41%	11/35=31%
Brazil	13.0%	-36.0%	61.0%	4/8=50%	3/8=38%
Philip.	13.0%	-38.0%	65.0%	2/6=33%	1/5=20%
Canada	16.0%	-23.0%	54.0%	3/10=30%	1/7=14%
Poland	17.0%	-15.0%	48.0%	9/18=50%	6/18=33%
Australia	21.0%	-38.0%	81.0%	2/4=50%	2/7=29%
US	26.0%	1.0%	52.0%	8/21=38%	2/17=12%
Portugal	42.0%	-20.0%	100%	2/3=67%	2/8=25%
Taiwan	45.0%	11.0%	79.0%	6/11=55%	1/11=9%
Thailand	47.0%	-5.0%	98.0%	4/5=80%	2/6=33%
Israel	50.0%	-19.0%	100%	1/2=50%	0/2=0%
Malaysia	50.0%	-10.0%	100%	3/4=75%	1/4=25%
Hong_Kong	67.0%	13.0%	100%	2/3=67%	0/2=0%
Greece	75.0%	33.0%	100%	3/4=75%	0/4=0%
Argentina	80.0%	45.0%	100%	4/5=80%	0/5=0%
Singapore	100%	100%	100%	2/2=100%	0/1=0%
REGION					
Europe	19.0%	3.0%	35.0%	28/62=45%	19/72=26%
N_America	23.0%	2.0%	44.0%	11/31=35%	3/24=13%
S_America	38.0%	3.0%	73.0%	8/13=62%	3/13=23%
Asia	41.0%	20.0%	61.0%	21/35=60%	7/36=19%

TABLE 4.2 C
WEEK 48 HISTOLOGIC IMPROVEMENT
TRIAL 22

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
HBEAB					
Negative	9.0%	2.0%	17.0%	220/342=64%	190/346=55%
Positive	-6.0%	-49.0%	38.0%	6/12=50%	5/9=56%
HBEAG					
Negative	-25.0%	-83.0%	33.0%	3/6=50%	3/4=75%
Positive	9.0%	2.0%	17.0%	223/348=64%	192/351=55%
HBSAG					
Positive	9.0%	2.0%	16.0%	226/354=64%	195/355=55%
SUBTYPE					
AG	-100%	-100%	-100%	0/2=0%	3/3=100%
DG	-25.0%	-100%	56.0%	1/4=25%	1/2=50%
	-7.0%	-64.0%	50.0%	3/5=60%	4/6=67%
C	-1.0%	-14.0%	13.0%	72/111=65%	59/90=66%
AF	0.0%	0.0%	0.0%	0/2=0%	0/1=0%
A	12.0%	-2.0%	26.0%	60/94=64%	52/100=52%
B	12.0%	-4.0%	28.0%	46/68=68%	43/77=56%
D	19.0%	-2.0%	40.0%	22/37=59%	20/49=41%
F	23.0%	-12.0%	58.0%	13/20=65%	5/12=42%
Indeter.	27.0%	-6.0%	61.0%	8/9=89%	8/13=62%
LBASEB_Q					
<=1.99	17.0%	3.0%	32.0%	61/94=65%	40/84=48%
1.99-2.82	7.0%	-8.0%	21.0%	55/86=64%	52/91=57%
2.82-3.39	10.0%	-4.0%	24.0%	60/91=66%	48/86=56%
>3.39	2.0%	-13.0%	16.0%	50/83=60%	55/94=59%
LBASEP_Q					
<=8.48	16.0%	1.0%	30.0%	60/97=62%	38/82=46%
8.48-9.29	13.0%	-2.0%	27.0%	57/84=68%	52/94=55%
9.29-10.26	6.0%	-9.0%	21.0%	52/86=60%	49/90=54%
>10.26	3.0%	-12.0%	17.0%	57/87=66%	56/89=63%
PRIORINT					
N	9.0%	1.0%	17.0%	194/308=63%	167/310=54%
Y	7.0%	-12.0%	27.0%	32/46=70%	28/45=62%
PRIORLVD					
N	10.0%	3.0%	18.0%	221/344=64%	186/345=54%
Y	-40.0%	-76.0%	-4.0%	5/10=50%	9/10=90%

TABLE 4.2 C (cont.)
WEEK 48 HISTOLOGIC IMPROVEMENT
TRIAL 22

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
BLALT_Q					
<=71	14.0%	-1.0%	28.0%	47/93=51%	32/87=37%
71-103	9.0%	-5.0%	24.0%	53/86=62%	48/92=52%
103-172	0.0%	-15.0%	14.0%	52/85=61%	56/91=62%
>172	13.0%	0.0%	25.0%	74/90=82%	59/85=69%
ALTSTS_					
<1.25*ULN	-3.0%	-28.0%	22.0%	12/28=43%	15/33=45%
>=1.25*ULN	10.0%	2.0%	17.0%	214/326=66%	179/321=56%
ALTWHO					
0	-3.0%	-28.0%	22.0%	12/28=43%	15/33=45%
1	10.0%	-1.0%	21.0%	89/158=56%	72/157=46%
2	9.0%	-4.0%	21.0%	81/113=72%	66/105=63%
3	16.0%	-3.0%	34.0%	37/45=82%	28/42=67%
4	-6.0%	-41.0%	28.0%	7/10=70%	13/17=76%
AST_Q					
<=42	13.0%	-1.0%	27.0%	43/89=48%	33/94=35%
42-57	9.0%	-5.0%	23.0%	62/95=65%	51/91=56%
57-89	5.0%	-10.0%	19.0%	54/81=67%	54/87=62%
>89	7.0%	-7.0%	20.0%	67/89=75%	57/83=69%
INR_Q					
<=1.00	7.0%	-4.0%	17.0%	101/164=62%	95/173=55%
1.00-1.05	1.0%	-26.0%	28.0%	14/24=58%	16/28=57%
1.05-1.14	14.0%	-1.0%	28.0%	55/79=70%	46/82=56%
>1.14	12.0%	-4.0%	27.0%	56/87=64%	38/72=53%
PT_Q					
<=11.7	9.0%	-2.0%	21.0%	90/129=70%	80/132=61%
11.7-12.7	8.0%	-8.0%	24.0%	46/81=57%	32/66=48%
12.7-13.9	3.0%	-12.0%	19.0%	43/72=60%	44/78=56%
>13.9	16.0%	0.0%	31.0%	47/72=65%	39/79=49%
TBILI_Q					
<=0.6	5.0%	-6.0%	17.0%	79/127=62%	83/146=57%
0.6-0.7	13.0%	-6.0%	33.0%	30/49=61%	22/46=48%
0.7-1.0	11.0%	-3.0%	26.0%	55/90=61%	44/88=50%
>1.0	9.0%	-5.0%	24.0%	62/88=70%	46/75=61%

TABLE 4.2 C (cont.)
WEEK 48 HISTOLOGIC IMPROVEMENT
TRIAL 22

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
CREAT_Q					
<=0.8	13.0%	1.0%	25.0%	69/105=66%	74/141=52%
0.8-0.9	-2.0%	-18.0%	14.0%	39/75=52%	39/72=54%
0.9-1.0	19.0%	4.0%	34.0%	64/87=74%	38/70=54%
>1.0	1.0%	-14.0%	16.0%	54/87=62%	44/72=61%
BMI_Q					
<=21.1	3.0%	-11.0%	16.0%	58/92=63%	61/101=60%
21.1-23.5	2.0%	-13.0%	17.0%	59/91=65%	49/78=63%
23.5-26.2	18.0%	4.0%	33.0%	65/95=68%	40/80=50%
>26.2	11.0%	-4.0%	26.0%	44/76=58%	45/96=47%
HT_Q					
<=163	10.0%	-3.0%	23.0%	62/96=65%	59/108=55%
163-170	-5.0%	-19.0%	9.0%	47/95=49%	54/100=54%
170-176	21.0%	5.0%	36.0%	60/85=71%	34/68=50%
>176	12.0%	-2.0%	27.0%	57/78=73%	48/79=61%
WT_Q					
<=59	8.0%	-6.0%	22.0%	59/90=66%	57/99=58%
59-68	-2.0%	-16.0%	13.0%	53/90=59%	51/84=61%
68-78	12.0%	-3.0%	26.0%	69/103=67%	42/76=55%
>78	17.0%	1.0%	32.0%	45/71=63%	45/96=47%
BPDIA_Q					
<=70	5.0%	-7.0%	17.0%	86/135=64%	81/138=59%
70-76	-3.0%	-21.0%	16.0%	36/53=68%	31/44=70%
76-80	10.0%	-3.0%	23.0%	66/104=63%	54/101=53%
>80	21.0%	4.0%	38.0%	38/62=61%	29/72=40%
BPSYS_Q					
<=110	9.0%	-3.0%	21.0%	77/115=67%	76/132=58%
110-120	0.0%	-13.0%	14.0%	65/108=60%	60/100=60%
120-130	15.0%	-1.0%	32.0%	45/69=65%	33/66=50%
>130	17.0%	0.0%	35.0%	39/62=63%	26/57=46%

TABLE 4.2 C (cont.)
WEEK 48 HISTOLOGIC IMPROVEMENT
TRIAL 22

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
CNTRY					
Israel	-25.0%	-68.0%	18.0%	5/10=50%	6/8=75%
Switzerl.	-25.0%	-100%	56.0%	1/2=50%	3/4=75%
Hong_Kong	-24.0%	-57.0%	9.0%	7/15=47%	12/17=71%
US	-9.0%	-32.0%	14.0%	18/32=56%	24/37=65%
Denmark	0.0%	-75.0%	75.0%	1/3=33%	1/3=33%
Italy	0.0%	-53.0%	53.0%	4/6=67%	4/6=67%
Slovakia	0.0%	0.0%	0.0%	0/1=0%	0/1=0%
Australia	3.0%	-24.0%	29.0%	16/24=67%	16/25=64%
Korea	3.0%	-22.0%	29.0%	18/23=78%	15/20=75%
Taiwan	6.0%	-12.0%	24.0%	38/55=69%	33/52=63%
Malaysia	7.0%	-29.0%	43.0%	9/14=64%	8/14=57%
Philip.	10.0%	-18.0%	38.0%	10/24=42%	7/22=32%
Russia	13.0%	-21.0%	47.0%	9/15=60%	8/17=47%
Indonesia	17.0%	-27.0%	60.0%	6/9=67%	5/10=50%
Poland	18.0%	-3.0%	40.0%	26/34=76%	21/36=58%
Singapore	20.0%	-30.0%	69.0%	5/8=63%	3/7=43%
Brazil	23.0%	-3.0%	48.0%	16/28=57%	9/26=35%
Argentina	24.0%	-6.0%	55.0%	15/21=71%	8/17=47%
Holland	25.0%	-40.0%	90.0%	3/4=75%	2/4=50%
Canada	26.0%	-6.0%	59.0%	11/15=73%	8/17=47%
Peru	50.0%	-19.0%	100%	1/2=50%	0/2=0%
UK	60.0%	10.0%	100%	4/5=80%	1/5=20%
Belgium	75.0%	33.0%	100%	3/4=75%	0/3=0%
REGION					
N_America	2.0%	-17.0%	21.0%	29/47=62%	33/55=60%
Asia	4.0%	-6.0%	14.0%	109/172=63%	99/167=59%
Europe	14.0%	0.0%	29.0%	56/84=67%	46/88=52%
S_America	25.0%	6.0%	44.0%	32/51=63%	17/45=38%

TABLE 4.2 D
WEEK 48 HISTOLOGIC IMPROVEMENT
TRIAL 27

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
HBEAB					
Negative	50.0%	-19.0%	100%	1/2=50%	0/1=0%
Positive	8.0%	1.0%	16.0%	207/323=64%	174/312=56%
HBEAG					
Negative	8.0%	0.0%	15.0%	206/322=64%	174/309=56%
Positive	50.0%	-19.0%	100%	1/2=50%	0/4=0%
HBSAG					
Positive	8.0%	1.0%	16.0%	208/325=64%	174/312=56%
SUBTYPE					
B	-4.0%	-24.0%	15.0%	24/46=52%	34/60=57%
F	0.0%	0.0%	0.0%	1/1=100%	2/2=100%
A	6.0%	-18.0%	30.0%	17/33=52%	15/33=45%
C	7.0%	-10.0%	24.0%	42/57=74%	34/51=67%
	10.0%	-28.0%	47.0%	8/12=67%	8/14=57%
D	11.0%	0.0%	22.0%	100/157=64%	71/135=53%
DG	13.0%	-42.0%	67.0%	3/4=75%	5/8=63%
Indeter.	38.0%	4.0%	71.0%	9/9=100%	5/8=63%
BC	100%	100%	100%	2/2=100%	0/1=0%
E	100%	100%	100%	1/1=100%	0/1=0%
LBASEB_Q					
<=0.48	-5.0%	-20.0%	11.0%	45/81=56%	47/78=60%
0.48-1.13	12.0%	-3.0%	27.0%	45/74=61%	42/86=49%
1.13-2.03	15.0%	0.0%	30.0%	64/92=70%	37/68=54%
2.03	10.0%	-5.0%	25.0%	54/78=69%	48/81=59%
LBASEP_Q					
<=6.64	2.0%	-13.0%	17.0%	50/82=61%	47/80=59%
6.64-7.51	7.0%	-9.0%	22.0%	48/81=59%	41/78=53%
7.51-8.74	22.0%	7.0%	37.0%	55/80=69%	37/79=47%
>8.74	3.0%	-12.0%	17.0%	55/82=67%	49/76=64%
PRIORINT					
N	8.0%	0.0%	16.0%	181/283=64%	154/274=56%
Y	13.0%	-8.0%	34.0%	27/42=64%	20/39=51%
PRIORLVD					
N	8.0%	1.0%	16.0%	204/316=65%	169/301=56%
Y	3.0%	-40.0%	46.0%	4/9=44%	5/12=42%

TABLE 4.2 D (cont.)
WEEK 48 HISTOLOGIC IMPROVEMENT
TRIAL 27

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
BLALT_Q					
<=67	-4.0%	-19.0%	11.0%	44/81=54%	46/79=58%
67-106	4.0%	-11.0%	19.0%	52/82=63%	47/79=59%
106-172	15.0%	0.0%	31.0%	52/81=64%	38/78=49%
>172	18.0%	4.0%	33.0%	60/81=74%	43/77=56%
ALTSTS_					
<1.25*ULN	-14.0%	-39.0%	12.0%	13/29=45%	17/29=59%
>=1.25*ULN	11.0%	3.0%	19.0%	195/296=66%	157/284=55%
ALTWHO					
0	-14.0%	-39.0%	12.0%	13/29=45%	17/29=59%
1	5.0%	-7.0%	17.0%	86/130=66%	78/128=61%
2	11.0%	-2.0%	24.0%	68/112=61%	51/103=50%
3	20.0%	0.0%	40.0%	31/43=72%	22/42=52%
4	36.0%	2.0%	70.0%	10/11=91%	6/11=55%
AST_Q					
<=42	4.0%	-12.0%	19.0%	50/88=57%	41/77=53%
42-60	-6.0%	-21.0%	9.0%	51/79=65%	55/78=71%
60-96	20.0%	5.0%	35.0%	52/78=67%	38/81=47%
>96	17.0%	2.0%	32.0%	55/80=69%	40/77=52%
INR_Q					
<=1.00	11.0%	-1.0%	23.0%	76/114=67%	75/135=56%
1.00-1.10	-2.0%	-16.0%	13.0%	57/94=61%	51/82=62%
1.10-1.19	-1.0%	-22.0%	21.0%	24/39=62%	23/37=62%
>1.19	23.0%	7.0%	39.0%	51/78=65%	25/59=42%
PT_Q					
<=11.7	3.0%	-8.0%	15.0%	84/129=65%	87/141=62%
11.7-12.6	1.0%	-17.0%	18.0%	35/54=65%	43/67=64%
12.6-13.9	24.0%	6.0%	41.0%	52/77=68%	21/48=44%
>13.9	17.0%	-1.0%	34.0%	37/65=57%	23/57=40%
TBILI_Q					
<=0.6	11.0%	-1.0%	24.0%	81/120=68%	69/123=56%
0.6-0.8	-1.0%	-17.0%	15.0%	44/79=56%	43/76=57%
0.8-1.0	-8.0%	-27.0%	11.0%	26/45=58%	40/61=66%
>1.0	29.0%	12.0%	45.0%	57/81=70%	22/53=42%

TABLE 4.2 D (cont.)
WEEK 48 HISTOLOGIC IMPROVEMENT
TRIAL 27

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
CREAT_Q					
<=0.8	9.0%	-3.0%	21.0%	84/134=63%	58/108=54%
0.8-0.9	10.0%	-6.0%	25.0%	46/69=67%	45/79=57%
0.9-1.0	11.0%	-8.0%	29.0%	38/58=66%	28/51=55%
>1.0	5.0%	-11.0%	21.0%	40/64=63%	43/75=57%
BMI_Q					
<=22.7	9.0%	-5.0%	23.0%	65/91=71%	52/83=63%
22.7-25.0	2.0%	-13.0%	18.0%	50/76=66%	50/79=63%
25.0-27.4	10.0%	-6.0%	25.0%	45/77=58%	38/78=49%
>27.4	13.0%	-3.0%	28.0%	48/81=59%	34/73=47%
HT_Q					
<=163	12.0%	-2.0%	26.0%	65/99=66%	48/89=54%
163-168	-3.0%	-19.0%	13.0%	38/62=61%	52/81=64%
168-175	11.0%	-4.0%	26.0%	54/83=65%	45/83=54%
>175	15.0%	-2.0%	31.0%	51/81=63%	29/60=48%
WT_Q					
<=63	3.0%	-12.0%	17.0%	61/92=66%	49/77=64%
63-71	17.0%	3.0%	32.0%	48/63=76%	56/95=59%
71-80	8.0%	-7.0%	23.0%	57/94=61%	41/78=53%
>80	11.0%	-6.0%	27.0%	42/76=55%	28/63=44%
BPDIA_Q					
<=70.0	11.0%	-2.0%	24.0%	78/118=66%	59/107=55%
70.0-80.0	7.0%	-5.0%	19.0%	84/130=65%	71/124=57%
>80.5	6.0%	-9.0%	21.0%	46/77=60%	44/82=54%
BPSYS_Q					
<=110	5.0%	-9.0%	19.0%	57/93=61%	51/91=56%
110-120	16.0%	1.0%	31.0%	63/87=72%	41/73=56%
120-130	2.0%	-14.0%	18.0%	43/69=62%	41/68=60%
>130	9.0%	-7.0%	24.0%	45/76=59%	41/81=51%

TABLE 4.2 D (cont.)
WEEK 48 HISTOLOGIC IMPROVEMENT
TRIAL 27

		95% Limit		Mean Change	
Covariate	Diff	Lower	Upper	ETV/r	LVD
CNTRY					
Denmark	-100%	-100%	-100%	0/1=0%	1/1=100%
Hungary	-50.0%	-100%	19.0%	1/2=50%	1/1=100%
Canada	-39.0%	-79.0%	1.0%	4/8=50%	8/9=89%
Taiwan	-13.0%	-33.0%	8.0%	22/42=52%	28/43=65%
US	-9.0%	-41.0%	23.0%	10/20=50%	10/17=59%
Hong_Kong	-7.0%	-32.0%	18.0%	11/13=85%	11/12=92%
Israel	-7.0%	-32.0%	19.0%	14/30=47%	16/30=53%
Argentina	0.0%	-61.0%	61.0%	3/5=60%	3/5=60%
Czech_R	0.0%	0.0%	0.0%	2/2=100%	2/2=100%
Russia	3.0%	-37.0%	43.0%	6/14=43%	4/10=40%
Poland	10.0%	-38.0%	57.0%	6/9=67%	4/7=57%
Australia	14.0%	-21.0%	49.0%	9/14=64%	8/16=50%
Italy	14.0%	-25.0%	52.0%	7/11=64%	7/14=50%
Greece	15.0%	-22.0%	52.0%	6/13=46%	4/13=31%
Turkey	15.0%	-7.0%	37.0%	24/31=77%	20/32=63%
Germany	20.0%	-18.0%	59.0%	9/12=75%	6/11=55%
Switzerl.	20.0%	-30.0%	69.0%	5/8=63%	3/7=43%
Portugal	23.0%	-29.0%	76.0%	5/6=83%	3/5=60%
Brazil	25.0%	1.0%	50.0%	19/30=63%	11/29=38%
Singapore	25.0%	-21.0%	71.0%	6/8=75%	4/8=50%
Thailand	32.0%	6.0%	58.0%	18/20=90%	11/19=58%
Slovakia	42.0%	-26.0%	100%	3/4=75%	1/3=33%
Malaysia	48.0%	-1.0%	96.0%	7/8=88%	2/5=40%
Belgium	50.0%	1.0%	99.0%	2/4=50%	0/1=0%
Holland	50.0%	1.0%	99.0%	2/2=100%	2/4=50%
Spain	50.0%	1.0%	99.0%	4/4=100%	2/4=50%
UK	67.0%	13.0%	100%	2/3=67%	0/3=0%
REGION					
N_America	-20.0%	-46.0%	5.0%	14/28=50%	19/27=70%
Asia	7.0%	-5.0%	20.0%	74/106=70%	65/104=63%
Europe	11.0%	0.0%	23.0%	98/156=63%	76/148=51%
S_America	22.0%	-1.0%	45.0%	22/35=63%	14/34=41%

5. Statistical Reviewer's Conclusions

The applicant submitted four randomized, controlled pivotal clinical trials with entecavir for this application: trial 14, originally planned as a phase 2 study, and trials 22, 26, and 27, all phase 3 trials. Two of the trials, 14 and 26, enrolled subjects who were refractory to LVD, defined as either HBV DNA > 5 log copies/mL while on LVD or evidence of LVD^R substitutions in the viral DNA. For these subjects, a dose of 1 mg qd entecavir (ETV) was used. The other two trials, 22 and 27, enrolled subjects who were nucleoside naive (fewer than 12 weeks of treatment). Trial 22 recruited HBeAg+ subjects; trial 27 recruited HBeAg-/HBeAb+ subjects. For these subjects, a dose of .5 mg qd entecavir was used. The control subjects in all trials received 100 mg qd of lamivudine (LVD).

The trials were planned as superiority trials in the LVD experienced populations and as non-inferiority trials in the LVD naive populations. All trials compared proportions of subjects with HBV DNA below limit of quantitation (BLQ) at the final visit (week 24 for trial 14 and week 48 for the three planned pivotal trials). This was the primary endpoint in trial 14 and a secondary endpoint in trials 22, 26, and 27. The latter three trials compared proportions of subjects with Knodell necrosis score improving by at least two points between baseline and week 48 biopsies.

In all four trials, subjects on ETV had statistically and clinically superior responses to subjects on LVD. This was even true in the two trials intended as non-inferiority trials. The ETV superiority was demonstrated for both primary endpoints, improvement in Knodell necrosis score, and secondary endpoints, suppression of HBV DNA to BLQ and suppression of ALT to below upper limit of normal (ULN). These findings were robust to sensitivity analyses conducted on the missing data.

The applicant also submitted a small trial, trial 38, in which HBV and HIV co-infected patients were enrolled. The findings on primary and secondary endpoints were compatible with those in trials 14, 22, 26, and 27. Because the sample size in

this trial was small, no treatment effects were statistically significant. Details on the review of this trial are not reproduced here.

The FDA statistical reviewer concludes that the applicant has established that entecavir is an effective treatment of hepatitis B, at a dose of 1 mg qd in LVD refractory subjects and at a dose of .5 mg qd in LVD naive subjects.

Concur: Dr. Soon
cc:
Archival NDA #21-797
HFD-530
HFD-530/Dr. Birnkrant
HFD-530/Dr. Murray
HFD-530/Dr. Lewis
HFD-530/Dr. Laessig
HFD-530/Ms. Holloman
HFD-725/Dr. Hammerstrom
HFD-700/Dr. Anello
HFD-725/Dr. Huque
HFD-725/Ms. Broadwater

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/s/

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3/28/05 11:25:24 AM
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