STATISTICAL REVIEW AND EVALUATION

NDA#:	21-797/S-018, 21-798/S-019
NAME OF DRUG:	Barraclude (Entecavir)
INDICATION:	Treatment of Chronic HBV Infection in Children
APPLICANT:	Bristol-Myers-Squibb
SUBMISSION DATE:	Oct. 16, 2013
TYPE OF REVIEW:	Clinical
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NDA#: 21-797, 21-798

1. Executive Summary

For this application, the applicant submitted one randomized, placebo controlled phase 3 clinical trial with entecavir (ETV), trial AI463189 (189) and one single arm trial, AI463028 (028). The primary objective of study 189 was to compare the efficacy of entecavir to that of placebo control in pediatric patients age 2-18 years with chronic hepatitis B who HBeAg positive and nucleot(s)ide naïve. The trial 189 an ongoing randomized, double-blind, placebo controlled, multi-center trial, conducted in North America, Argentina, and Europe. Subjects were randomly assigned in a 2:1 ratio to ETV, dosed at .015mg/kg of body weight per day, or placebo for 96 weeks with the primary endpoint being evaluated at week 48.

In this trial, entecavir at .015 mg/kg has been confirmed to be a clinically effective treatment for the treatment of chronic hepatitis B in children aged 2 to 18 years. The pattern of efficacy already demonstrated in adults was confirmed in the randomized, controlled trial conducted in children. The ETV regimen was statistically significantly and clinically meaningfully more effective than placebo in suppressing viral load at week 48 and in inducing ALT normalization at the same time point. ETV was estimated to have slightly more than 40% success rates than placebo on both endpoints. With respect to E antigen sero-conversion, it was estimated to about 10% better than placebo but this estimate fell slightly short of statistical significance. This may, of course, be a consequence of the small sample size in the pediatric study. Results in adult studies suggest it is effective with respect to this endpoint as well.

The efficacy was estimated to be consistent across sex, race, age and other sub-groups with one exception. Children with genotype D infections had much lower success rates with respect to all three endpoints than did children with genotypes A, B, or C. FDA statistical analyses suggest three conclusions. First and most important, ETV was estimated to be superior to placebo in all genotypes. Second, there was an estimated interaction between genotype, baseline viral load, and treatment. Third, part of the observed lower success rate was due to the higher baseline viral load in genotype D, as conjectured by the applicant. Nonetheless, the choice of ETV for treatment even in this sub-group seems to

be reasonable on the grounds of efficacy unless there was a substantial safety concern.

2. Introduction

2.1 Overview

For this application, the applicant submitted one randomized, placebo controlled phase 3 clinical trial with entecavir (ETV), trial AI463189 (189) and one single arm trial, AI463028 (028).

2.2 Data Sources

2.2.1 Objectives in Trials

The primary objective of study 189 was to compare the efficacy of entecavir to that of placebo control in pediatric patients age 2-18 years with chronic hepatitis B who HBeAg positive and nucleot(s)ide naïve.

2.2.2 Summary of Study Design

Trial 189 is an ongoing randomized, double-blind, placebo controlled, multi-center trial, conducted at 44 centers in North America, Argentina, and Europe. Subjects were randomly assigned in a 2:1 ratio to ETV, dosed at .015mg/kg of body weight per day, or placebo for 96 weeks with the primary endpoint being evaluated at week 48. Randomization was stratified by age: 2-6 years, 6-12 years, and 12-18 years. 180 subjects were randomized, of whom the first 123 constitute the primary cohort.

Subjects will be evaluated for viral suppression and HBeAg seroconversion at week 48. At week 52, subjects will either be continued on their assigned and blinded therapy until week 96 if they achieved HBeAg seroconversion by week 48 or switched to open label ETV if they did not achieve HBeAg seroconversion. This latter group will be re-evaluated for seroconversion at week 96. Seroconverters at this later time point will continue ETV to week 144. Non-converters at both week 48 and week 96, will stop at week 96 if they were initially on ETV and will continue on open-label ETV until week 144 if they were initially on placebo. This last group will be evaluated again at week 144 and either stopped

if they don't seroconvert or continued on open-label ETV until week 192 if they do seroconvert for the first time at week 144.

Briefly, all subjects who fail on placebo will get at least 96 weeks of open label ETV and, if they seroconvert on ETV, will get 48 weeks of ETV beyond seroconversion.

2.2.3 Patient Accounting and Baseline Characteristics

228 patients were enrolled in trial 189, of whom 180 were randomized. Table 2.2.3 A summarizes the primary reasons for discontinuation.

TABLE 2.2.3 A
PATIENT STATUS, TRIAL 189

	ETV	Placebo
Randomized	120	60
Discontinued		
Before Week 48	3	4
Week 48-96	1	0
Completed	25	3
Continuing	91	53

The subjects in trial 202 were enrolled at 52 centers in America and Argentina. There were 319 patients at 49 US sites and 21 patients at 3 Argentine sites. The subjects in trial 213 were enrolled at 57 centers in Canada, South America, Europe, and Australia. There were 217 patients at 40 European sites, 10 patients at 7 Canadian sites, 80 patients at 6 South American sites, and 27 patients at 4 Australian sites.

Table 2.2.3 C compares the baseline characteristics of trial 189.

TABLE 2.2.3 C

BASELINE CHARACTERISTICS

CHARACTERISTIC	ETV	Placebo
Age		
2-6	27	14
6-12	31	15
12-18	62	31
# Male	78	31
Race		
Asian	57	30
Black	14	2
White	44	27
Other	5	1
Geographic Region		
Asia	25	13
Europe	53	33
N.America	41	14
S.America	1	0
Baseline HBV DNA		
<8 log IU/ml	47	31
>= 8 log IU/ml	73	29
HB Surface Ag Positive	120	59
HB E Ab Negative	116	59
HBV Genotype		
A	22	11
B	17	11
C	31	16
D	42	20
Other	8	2
Baseline ALT		
<= 2 ULN	23	17
2-5 ULN	74	39
> 5 ULN	23	4
Route of Transmission		
Mother-Child	70	29
Household Contact	7	1
Transfusion	7	4
Unknown	36	26

2.2.4 Summary of Methods of Assessment

2.2.4.1 Schedule of Measurements

Patients had HBV DNA and HBeAg serology measured every 48 weeks out to end of study, which might be as late as week 192. Sparse PK data was collected at weeks 4, 12, 24, and 48.

2.2.4.2 Assessment of Treatment Effects

The primary analysis used the endpoint calculated for the initial cohort of 123 patients. The primary endpoint was the percentage of subjects who achieved, at week 48, the combination of 1)HBV DNA <50 IU/ml (=300c/ml) by the COBAS Taqman assay and 2)HBeAg seroconversion, defined as HBeAg undetectable plus HBeAb detectable. Subjects who discontinued prior to week 48 or were missing either or both of their week 48 HBV DNA and HBeAg serology measurements were classified as failures. A sensitivity analysis was conducted with such non-completers deleted from the analysis rather than counted as failures.

2.2.5 Summary of Statistical Analysis

The primary endpoint was analyzed by Cochran-Mantel-Haenszel test, stratified by the age categories used in the randomization. The primary analysis used missing data as failures; a sensitivity analysis used missing data as discarded from the analysis.

2.2.6 Summary of Applicant's Results

The reported results in trial 189 are given in table 2.2.6 A. This table gives the observed number and percent of subjects meeting the primary endpoint and four important secondary endpoints. It also gives the 95% confidence interval for difference between ETV and placebo and the p-value for the test of the arms being different. The confidence interval and p-value are computed adjusting for stratification by age. The limit of quantitation (LOQ) for the HBV DNA assay is 29IU/ml.

TABLE 2.2.6 A
PERCENT SUCCESFUL, WEEK 48, TRIAL 189
PRIMARY COHORT, 123 SUBJECTS

	ETV	Placebo	95% Interval on Difference	P-value P-value
HBV DNA<50+ Seroconversion	20/82=24%	1/41=2.4%	9.1%, 31.4%	.005
HBV DNA<50	38/82=46%	1/41=2.4%	29%, 54%	<.0001
ALT Normalization	55/82=67%	9/41=22%	29%, 61%	<.0001
HBV DNA<LOQ	35/82=43%	1/41=2.4%	26%, 51%	<.0001
Seroconversion	20/82=24%	5/41=12%	-1.5%, 26%	.11

There is no particular difference in viral suppression on ETV with respect to age or gender. In the three age cohorts and in both genders, the rate of viral suppression was in the range of 44% to 49%. (There is only 1 case of viral suppression on placebo so it is meaningless to examine the placebo rate by subgroup.) Viral suppression was lower (5/31=16%) in the genotype D subgroup.

There is also no particular difference in rate of ALT normalization on ETV with respect to age or gender. In all five age and gender subgroups, the rate of ALT normalization was in the range 60% to 78%.

HBeAg seroconversion is the one secondary endpoint on which the ETV superiority over placebo did not attain statistical significance. (From table 2.26 A one can see that all ETV subjects with seroconversion also had viral suppression but 4 placebo subjects had seroconversion without viral suppression.) The youngest age group had better seroconversion rates on ETV, 30% vs 21%-25% in the older groups. The seroconversion rate also went down with placebo, 18% for the 2-5 year olds vs 10% in the older groups. The seroconversion rates for males and females were comparable.

In general, endpoints on ETV were better in the groups with baseline covariates indicating better health, i.e. baseline ALT levels and baseline viral load. The poorer performance of genotype D subjects may be due to the higher levels of baseline HBV DNA in that group. There was not much evidence of treatment-covariate interaction.

2.2.7 Summary of Applicant's Conclusions

The applicant concluded that entecavir at .015 mg/kg for 48 weeks had demonstrable antiviral efficacy in subjects aged 2-17. The entecavir treated subjects performed better than the placebo subjects on both the composite primary endpoint of viral suppression and e-antigen seroconversion as well as on the individual endpoint of viral suppression, ALT normalization, and e-antigen seroconversion. The superiority was statistically significant on all endpoints except the last. In addition, the pediatric subjects with viral load <8 logs had success rates comparable to nucleos(t)ide naïve adults in the entecavir phase 3 trial.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Reproduction of Applicant's Analysis

The FDA statistical reviewer has confirmed the applicant's conclusions with respect to viral suppression, alt normalization, HBE seroconversion at week 48 for all subjects in the primary analysis population.

3.1.2 Efficacy in Genotype D

The applicant has observed that the one sub-group where there is noticeably less efficacy is genotype D. The applicant also observed that that sub-group had higher baseline HBV DNA levels than did the other genotypes. The FDA statistical reviewer has explored this potential interaction by doing a logistic regression of the binary variable of viral suppression at week 48 on the predictors of baseline HBV DNA, genotype, and their interaction.

The results of this logistic regression are summarized in table 3.1.2 A.

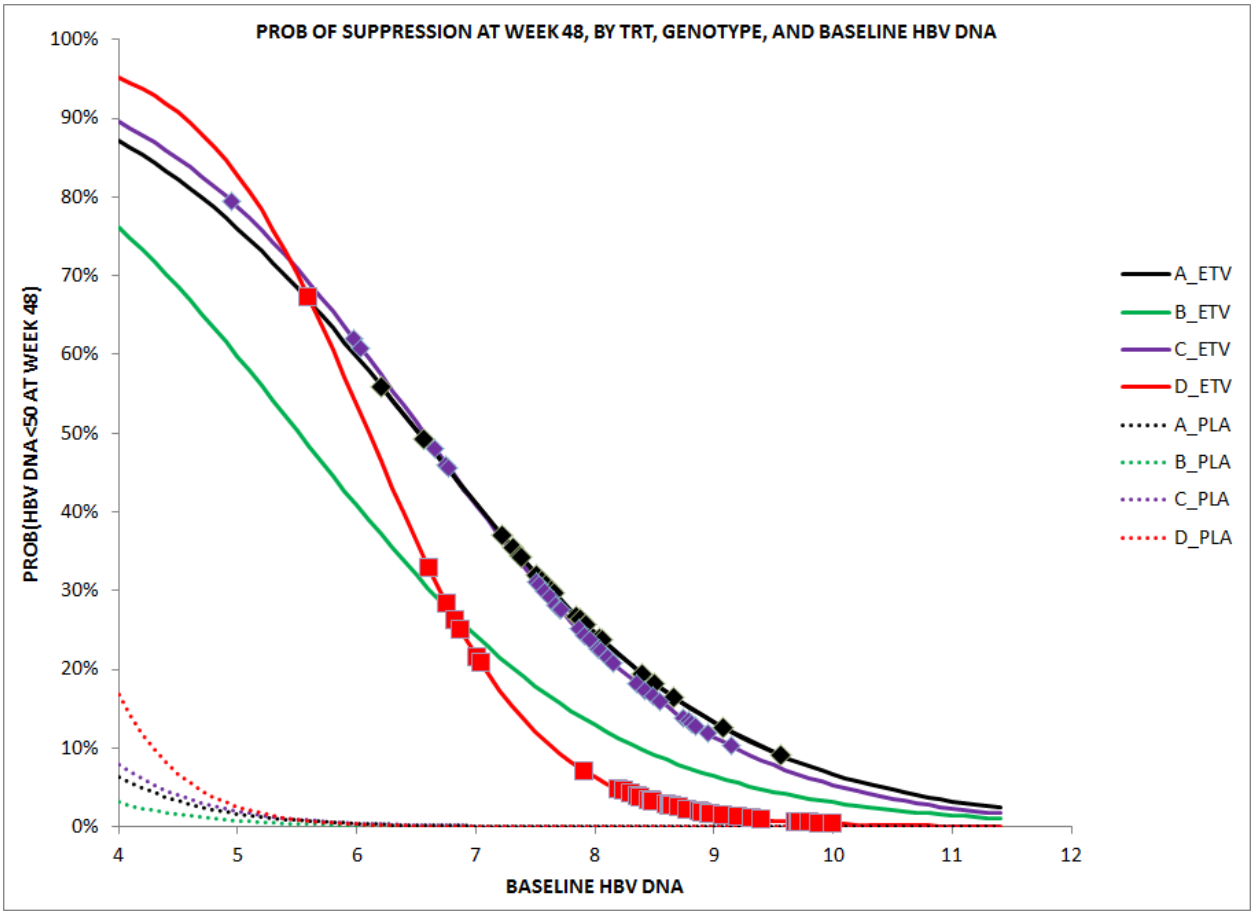
` TABLE 3.1.2 A
LOGISTIC REGRESSION OF VIRAL SUPPRESSION AT WEEK 48
ON TREATMENT, GENOTYPE AND BASELINE HBV DNA

Parameter		Estimate	Standard Error	P-value
Intercept		-7.9154	4.0151	0.0487
TRT	ETV	-2.0861	0.5831	0.0003
Baseline HBV DNA		1.3354	0.4989	0.0074
GENOTYPE	A	4.0644	5.6614	0.47
	B	1.9309	5.2470	0.71
	C	3.3116	4.9167	0.50
	D	-0.2405	5.0604	0.96
Base*GENOTYP	A	-0.5706	0.7105	0.42
	B	-0.2162	0.6532	0.74
	C	-0.4667	0.6115	0.44
	D	0.1615	0.6344	0.80

One can see from the p-values in the table that only the treatment and the baseline HBV DNA are statistically significant as a predictor of response. (The intercept only measures the extent to which the average probability of success is different from 50:50 so the p-value for the intercept is not interesting.)

The following graph shows the probability of viral suppression at week 48 as a function of treatment, baseline HBV DNA, and genotype as estimated in the above model. The four genotypes are indicated by color (black for A, green for B, purple for C, and, most conspicuously, red for D). The treatment is indicated by solid curves for barraclude and dotted curves for placebo. The fitted model does suggest that the effect of barraclude declines more rapidly for genotype D than for the other three genotypes as baseline HBV DNA increases but it still lies conspicuously above the dotted red curve for genotype D on placebo.

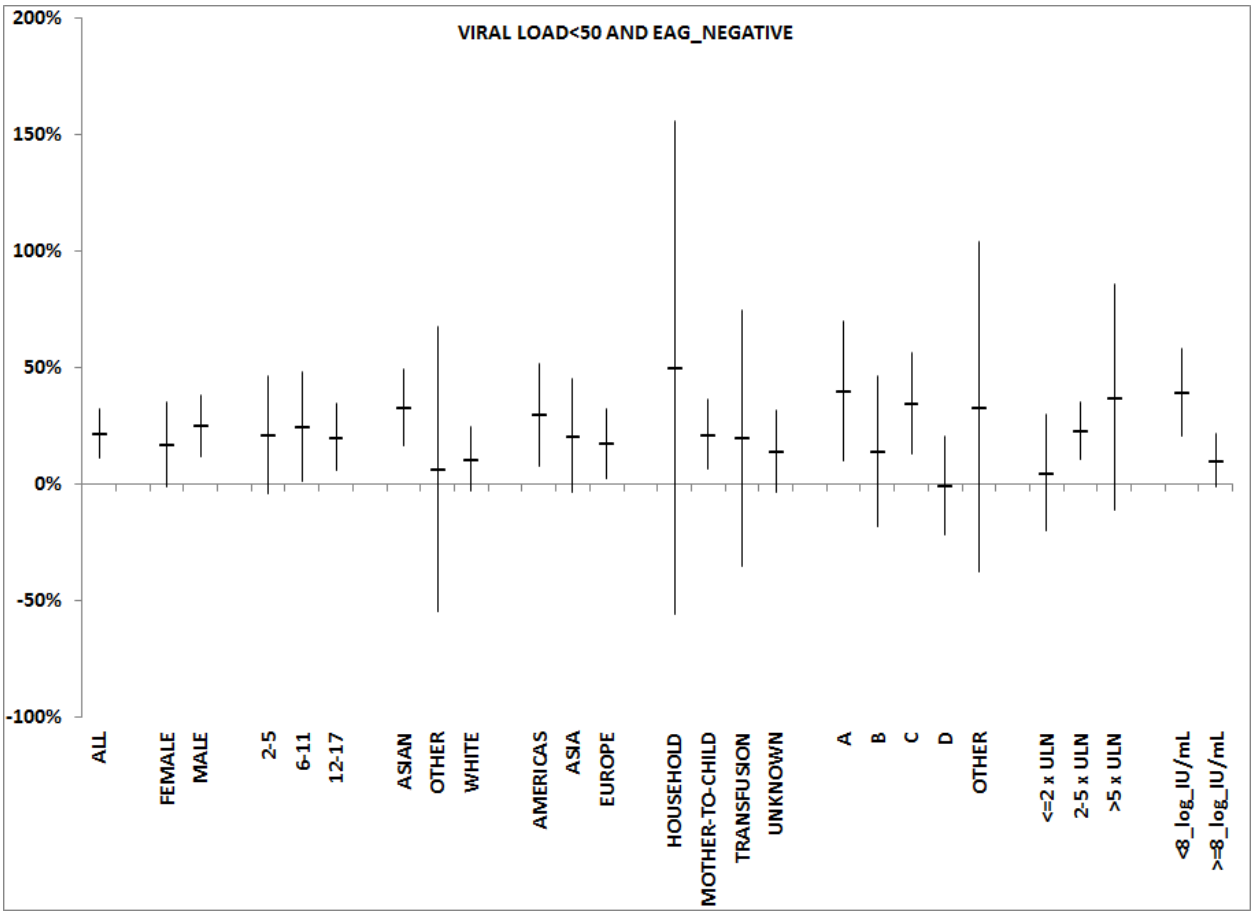
The graph also indicates how observations for genotype D are more toward the high end of baseline HBV DNA. There is a red square on the red genotype D, barraclude curve for every observation and a purple or black triangle on the curves for genotypes A and C, barraclude. One will notice that the dark triangles are more spread out between 5 and 10 logs for baseline HBV DNA while the red triangles are more heavily concentrated between 8 and 10 logs.

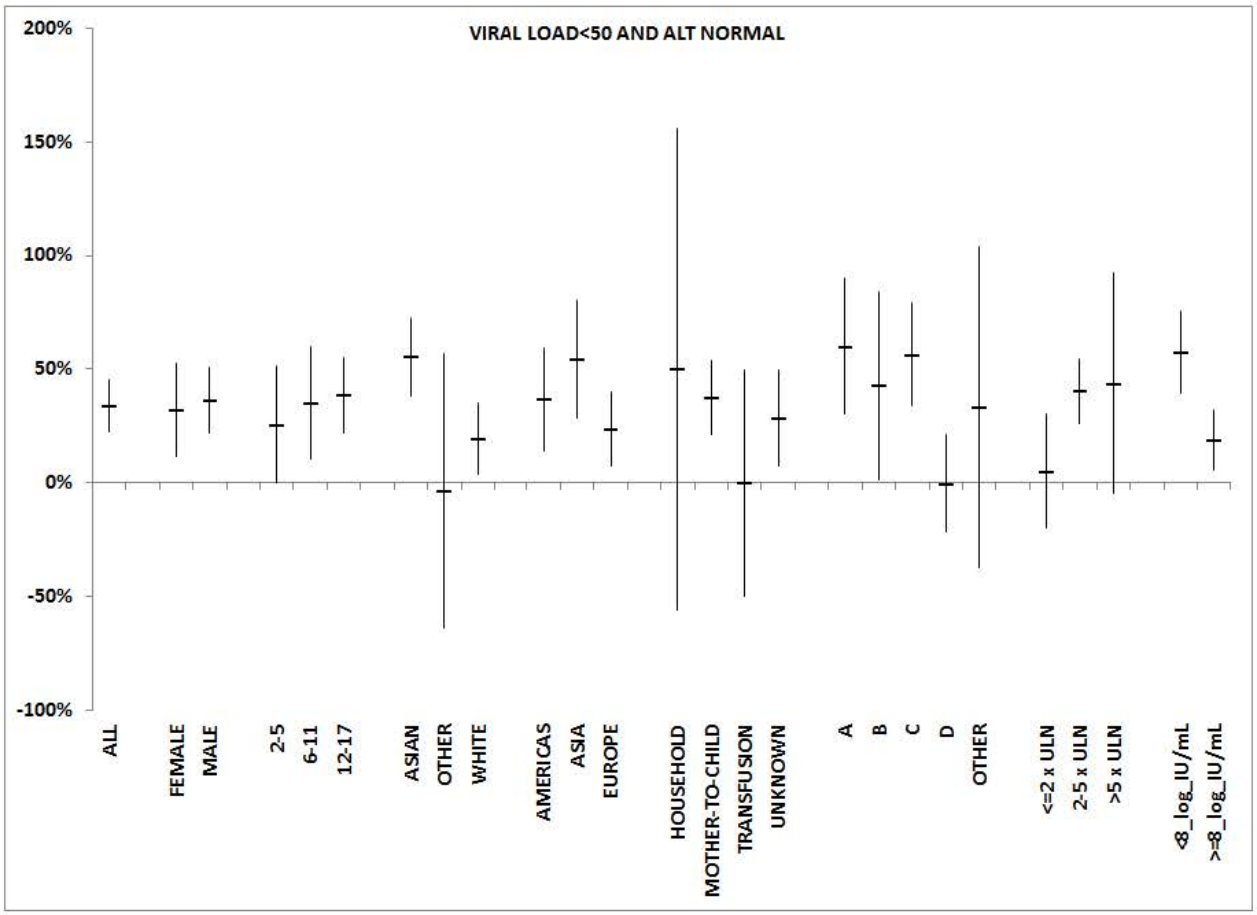


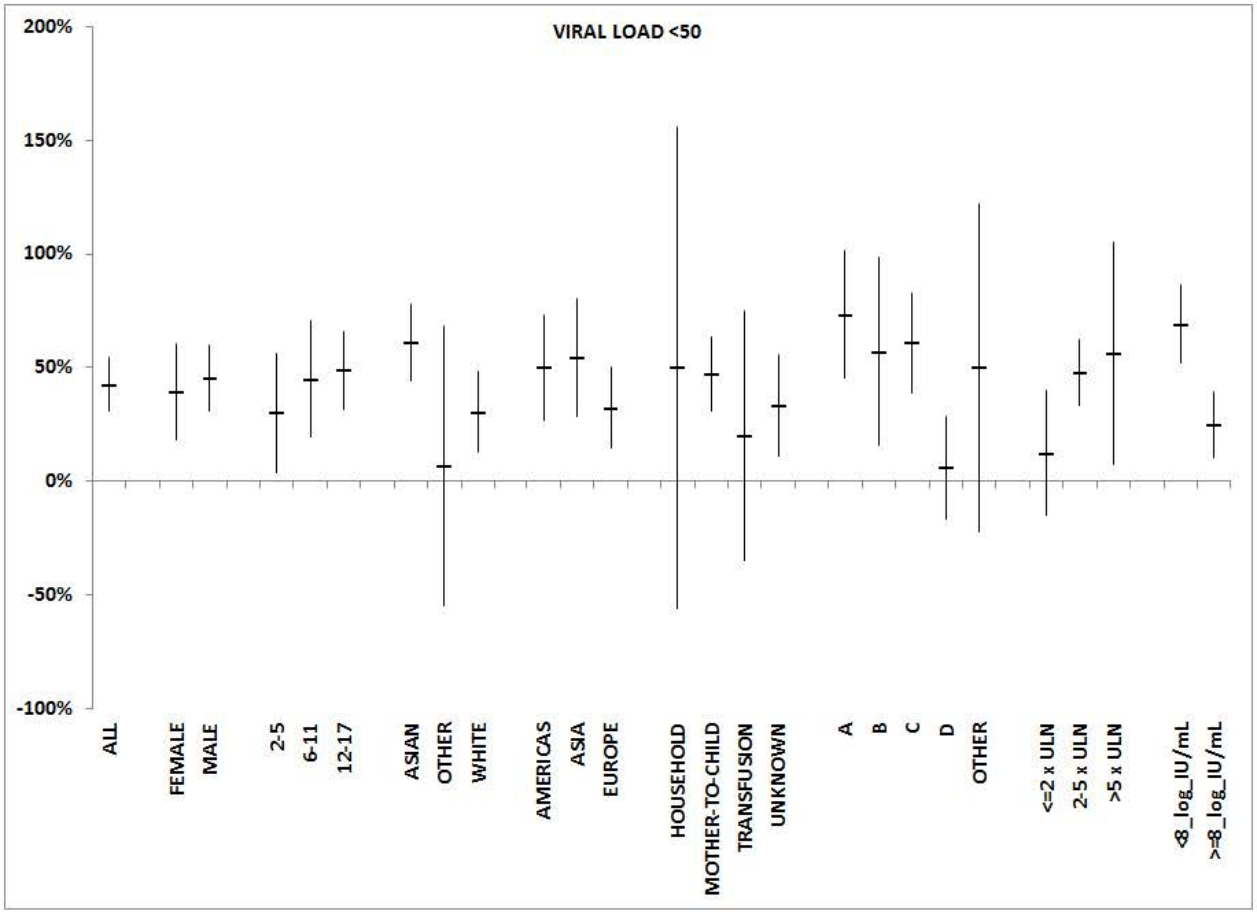
This simple fitted model still predicts that genotype D will do worse than the other genotypes for baseline HBV DNA > 7 logs.

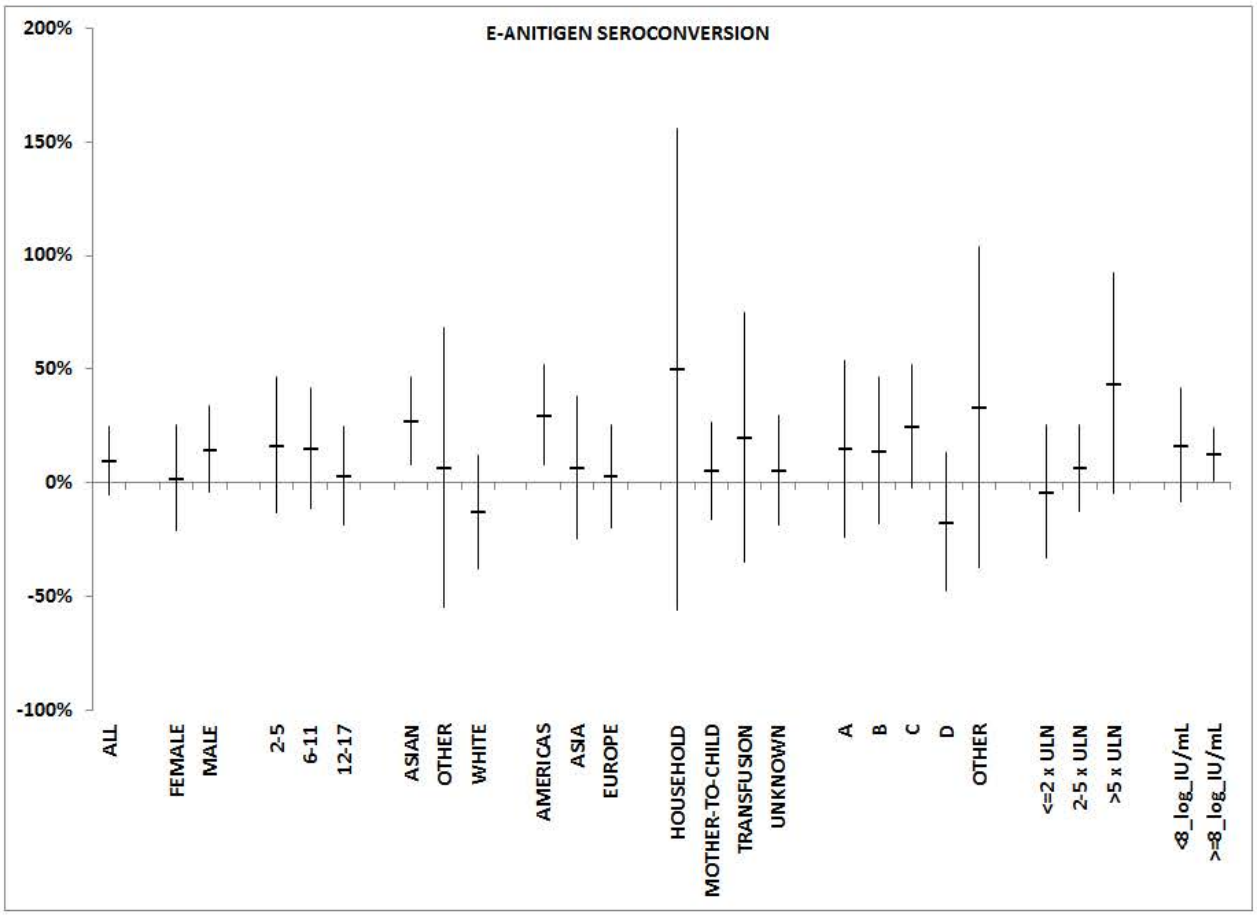
4. Results in Special Populations

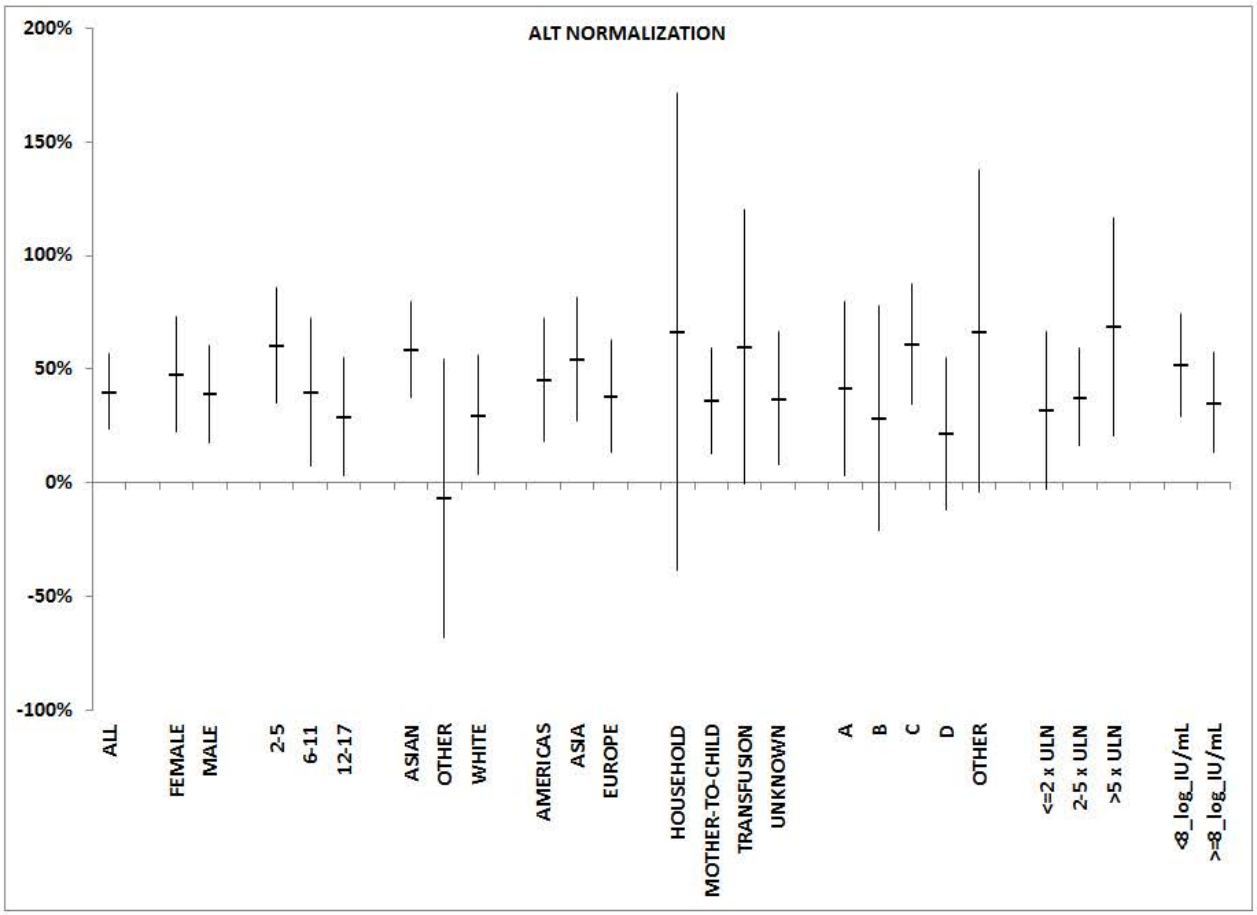
There was no evidence of clinically relevant interactions between treatment and any interesting covariates. Entecavir appeared to be clinically meaningfully superior to placebo for both sexes, all races with a reasonable number of subjects, all ages groups. Its superiority to control was also found at all levels of all baseline covariates examined, including baseline HBV DNA level and baseline ALT level. The numeric tables are given below in sections 4.1 and 4.2. The overall pattern of efficacy can be seen more easily in the following forest plots of the 95% confidence intervals for the various subgroups.




VIRAL LOAD<50 AND ALT NORMAL
200%
150%
100%
50%
0%
-50%
-100%
ALL
FEMALE
MALE
2-5
6-11
12-17
ASIAN
OTHER
WHITE
AMERICAS
ASIA
EUROPE
HOUSEHOLD
MOTHER-TO-CHILD
TRANSFUSION
UNKNOWN
A
B
C
D
OTHER
<=2 x ULN
2-5 x ULN
>5 x ULN
<8_log_IU/mL
>=8_log_IU/mL


VIRAL LOAD <50
200%
150%
100%
50%
0%
-50%
-100%
ALL
FEMALE
MALE
2-5
6-11
12-17
ASIAN
OTHER
WHITE
AMERICAS
ASIA
EUROPE
HOUSEHOLD
MOTHER-TO-CHILD
TRANSFUSION
UNKNOWN
A
B
C
D
OTHER
<=2 x ULN
2-5 x ULN
>5 x ULN
<8_log_IU/mL
>=8_log_IU/mL


E-ANITIGEN SEROCONVERSION
200%
150%
100%
50%
0%
-50%
-100%
ALL
FEMALE
MALE
2-5
6-11
12-17
ASIAN
OTHER
WHITE
AMERICAS
ASIA
EUROPE
HOUSEHOLD
MOTHER-TO-CHILD
TRANSFUSION
UNKNOWN
A
B
C
D
OTHER
<=2 x ULN
2-5 x ULN
>5 x ULN
<8_log_IU/mL
>=8_log_IU/mL



4.1 Gender, Race, and Age

Tables 4.1 A-E give the differences between ETV and placebo in percentage of subjects with viral suppression plus e-antigen seroconversion at week 48, with viral suppression plus ALT normalization, and with viral suppression, e-antigen seroconversio, and ALT normalization separately. The tables also give 95% confidence limits for those differences, and the percentages on ETV and on placebo. Results are given stratified by sex, race, and quartile of age. (In the tables in section 4, the counts in the sub-groups may not add up to the total count because sub-groups that are too small to give meaningful estimates have not been displayed.)

TABLE 4.1 A

VIR<50_AND_EAG_SEROCONVERSION_AT_WEEK_48

	ETV	PLACEBO	DIFF	LOWER	UPPER
ALL	20/82=24.39%	1/41=2.44%	21.95%	11.53%	32.38%
SEX					
FEMALE	6/27=22.22%	1/20=5.00%	17.22%	-1.14%	35.58%
MALE	14/55=25.45%	0/21=0.00%	25.45%	12.22%	38.69%
AGESTRAT					
2-5	7/23=30.43%	1/11=9.09%	21.34%	-4.00%	46.69%
6-11	5/20=25.00%	0/10=0.00%	25.00%	1.71%	48.29%
12-17	8/39=20.51%	0/20=0.00%	20.51%	6.11%	34.92%
RACE					
ASIAN	12/36=33.33%	0/23=0.00%	33.33%	16.82%	49.85%
OTHER	4/10=40.00%	1/3=33.33%	6.67%	-54.71%	68.05%
WHITE	4/36=11.11%	0/15=0.00%	11.11%	-2.60%	24.82%

TABLE 4.1 B

VIR<50_AND_ALT_NORMAL_AT_WEEK_48

	ETV	PLACEBO	DIFF	LOWER	UPPER
ALL	30/82=36.59%	1/41=2.44%	34.15%	22.70%	45.59%
SEX					
FEMALE	10/27=37.04%	1/20=5.00%	32.04%	11.47%	52.60%
MALE	20/55=36.36%	0/21=0.00%	36.36%	22.08%	50.65%
AGESTRAT					
2-5	8/23=34.78%	1/11=9.09%	25.69%	-0.14%	51.53%
6-11	7/20=35.00%	0/10=0.00%	35.00%	10.11%	59.89%
12-17	15/39=38.46%	0/20=0.00%	38.46%	21.73%	55.19%
RACE					
ASIAN	20/36=55.56%	0/23=0.00%	55.56%	38.26%	72.85%
OTHER	3/10=30.00%	1/3=33.33%	-3.33%	-63.77%	57.10%
WHITE	7/36=19.44%	0/15=0.00%	19.44%	3.64%	35.25%

TABLE 4.1 C

VIR<50_AT_WEEK_48

	ETV	PLACEBO	DIFF	LOWER	UPPER
ALL	37/82=45.12%	1/41=2.44%	42.68%	30.92%	54.44%
SEX					
FEMALE	12/27=44.44%	1/20=5.00%	39.44%	18.41%	60.48%
MALE	25/55=45.45%	0/21=0.00%	45.45%	30.77%	60.14%
AGESTRAT					
2-5	9/23=39.13%	1/11=9.09%	30.04%	3.84%	56.24%
6-11	9/20=45.00%	0/10=0.00%	45.00%	19.35%	70.65%
12-17	19/39=48.72%	0/20=0.00%	48.72%	31.60%	65.83%
RACE					
ASIAN	22/36=61.11%	0/23=0.00%	61.11%	44.11%	78.11%
OTHER	4/10=40.00%	1/3=33.33%	6.67%	-54.71%	68.05%
WHITE	11/36=30.56%	0/15=0.00%	30.56%	12.98%	48.13%

TABLE 4.1 D

EAG_SEROCONVERSION_AT_WEEK_48

	ETV	PLACEBO	DIFF	LOWER	UPPER
ALL	22/82=26.83%	7/41=17.07%	9.76%	-5.23%	24.74%
SEX					
FEMALE	6/27=22.22%	4/20=20.00%	2.22%	-21.30%	25.74%
MALE	16/55=29.09%	3/21=14.29%	14.81%	-4.38%	33.99%
AGESTRAT					
2-5	8/23=34.78%	2/11=18.18%	16.60%	-13.37%	46.57%
6-11	5/20=25.00%	1/10=10.00%	15.00%	-11.57%	41.57%
12-17	9/39=23.08%	4/20=20.00%	3.08%	-18.88%	25.04%
RACE					
ASIAN	13/36=36.11%	2/23=8.70%	27.42%	7.95%	46.88%
OTHER	4/10=40.00%	1/3=33.33%	6.67%	-54.71%	68.05%
WHITE	5/36=13.89%	4/15=26.67%	-12.78%	-37.85%	12.29%

TABLE 4.1 E

ALT_NORMAL_AT_WEEK_48

	ETV	PLACEBO	DIFF	LOWER	UPPER
ALL	53/82=64.63%	10/41=24.39%	40.24%	23.51%	56.97%
SEX					
FEMALE	21/27=77.78%	6/20=30.00%	47.78%	22.30%	73.26%
MALE	32/55=58.18%	4/21=19.05%	39.13%	17.87%	60.39%
AGESTRAT					
2-5	16/23=69.57%	1/11=9.09%	60.47%	35.13%	85.82%
6-11	12/20=60.00%	2/10=20.00%	40.00%	7.20%	72.80%
12-17	25/39=64.10%	7/20=35.00%	29.10%	3.34%	54.86%
RACE					
ASIAN	29/36=80.56%	5/23=21.74%	58.82%	37.57%	80.06%
OTHER	6/10=60.00%	2/3=66.67%	-6.67%	-68.05%	54.71%
WHITE	18/36=50.00%	3/15=20.00%	30.00%	3.99%	56.01%

4.2 Other Baseline Covariates

Tables 4.2 A-E give the information in the same order as tables 4.1 A-E. In this section, the stratifying variables are region, method of transmission, genotype, levels of baseline ALT, and levels of baseline HBV DNA. Genotype D is the one subgroup with a noticeably lower ETV effect.

TABLE 4.2 A

VIR<50_AND_EAG_SEROCONVERSION_AT_WEEK_48

	ETV	PLACEBO	DIFF	LOWER	UPPER
ALL	20/82=24.39%	1/41=2.44%	21.95%	11.53%	32.38%
REGION					
AMERICAS	9/30=30.00%	0/9=0.00%	30.00%	7.80%	52.20%
ASIA	5/18=27.78%	1/15=6.67%	21.11%	-3.13%	45.35%
EUROPE	6/34=17.65%	0/17=0.00%	17.65%	2.52%	32.77%
METHOD					
Household	3/6=50.00%	0/1=0.00%	50.00%	-55.85%	155.9%
Mother/Child	13/50=26.00%	1/22=4.55%	21.45%	6.50%	36.41%
Transfusion	1/5=20.00%	0/3=0.00%	20.00%	-34.84%	74.84%
Unknown	3/21=14.29%	0/15=0.00%	14.29%	-3.22%	31.79%
GENOTYPE					
A	6/15=40.00%	0/8=0.00%	40.00%	10.07%	69.93%
B	1/7=14.29%	0/7=0.00%	14.29%	-17.90%	46.47%
C	8/23=34.78%	0/14=0.00%	34.78%	13.03%	56.54%
D	3/31=9.68%	1/10=10.00%	-0.32%	-21.63%	20.99%
OTHER	2/6=33.33%	0/2=0.00%	33.33%	-37.55%	104.2%
BASEALT					
<=2_ULN	2/14=14.29%	1/11=9.09%	5.19%	-19.80%	30.19%
2-5_ULN	12/52=23.08%	0/27=0.00%	23.08%	10.55%	35.61%
>5_ULN	6/16=37.50%	0/3=0.00%	37.50%	-10.89%	85.89%
PCRCAT					
<8_LOG_IU/mL	15/34=44.12%	1/23=4.35%	39.77%	21.11%	58.43%
>=8_LOG_IU/mL	5/48=10.42%	0/18=0.00%	10.42%	-1.09%	21.92%

TABLE 4.2 B

VIR<50_AND_ALT_NORMAL_AT_WEEK_48

	ETV	PLACEBO	DIFF	LOWER	UPPER
ALL	30/82=36.59%	1/41=2.44%	34.15%	22.70%	45.59%
REGION					
AMERICAS	11/30=36.67%	0/9=0.00%	36.67%	13.83%	59.50%
ASIA	11/18=61.11%	1/15=6.67%	54.44%	28.63%	80.26%
EUROPE	8/34=23.53%	0/17=0.00%	23.53%	7.16%	39.89%
METHOD					
Household	3/6=50.00%	0/1=0.00%	50.00%	-55.85%	155.9%
Mother/Child	21/50=42.00%	1/22=4.55%	37.45%	21.24%	53.67%
Transfusion	0/5=0.00%	0/3=0.00%	0.00%	-49.70%	49.70%
Unknown	6/21=28.57%	0/15=0.00%	28.57%	7.22%	49.92%
GENOTYPE					
A	9/15=60.00%	0/8=0.00%	60.00%	30.07%	89.93%
B	3/7=42.86%	0/7=0.00%	42.86%	1.53%	84.19%
C	13/23=56.52%	0/14=0.00%	56.52%	34.05%	78.99%
D	3/31=9.68%	1/10=10.00%	-0.32%	-21.63%	20.99%
OTHER	2/6=33.33%	0/2=0.00%	33.33%	-37.55%	104.2%
BASEALT					
<=2_ULN	2/14=14.29%	1/11=9.09%	5.19%	-19.80%	30.19%
2-5_ULN	21/52=40.38%	0/27=0.00%	40.38%	26.11%	54.66%
>5_ULN	7/16=43.75%	0/3=0.00%	43.75%	-4.93%	92.43%
PCRCAT					
<8_LOG_IU/mL	21/34=61.76%	1/23=4.35%	57.42%	39.08%	75.76%
>=8_LOG_IU/mL	9/48=18.75%	0/18=0.00%	18.75%	5.35%	32.15%

TABLE 4.2 C

VIR<50_AT_WEEK_48

	ETV	PLACEBO	DIFF	LOWER	UPPER
ALL	37/82=45.12%	1/41=2.44%	42.68%	30.92%	54.44%
REGION					
AMERICAS	15/30=50.00%	0/9=0.00%	50.00%	26.67%	73.33%
ASIA	11/18=61.11%	1/15=6.67%	54.44%	28.63%	80.26%
EUROPE	11/34=32.35%	0/17=0.00%	32.35%	14.70%	50.01%
METHOD					
Household	3/6=50.00%	0/1=0.00%	50.00%	-55.85%	155.9%
Mother/Child	26/50=52.00%	1/22=4.55%	47.45%	31.10%	63.81%
Transfusion	1/5=20.00%	0/3=0.00%	20.00%	-34.84%	74.84%
Unknown	7/21=33.33%	0/15=0.00%	33.33%	11.22%	55.45%
GENOTYPE					
A	11/15=73.33%	0/8=0.00%	73.33%	45.37%	101.3%
B	4/7=57.14%	0/7=0.00%	57.14%	15.81%	98.47%
C	14/23=60.87%	0/14=0.00%	60.87%	38.68%	83.06%
D	5/31=16.13%	1/10=10.00%	6.13%	-16.53%	28.79%
OTHER	3/6=50.00%	0/2=0.00%	50.00%	-22.13%	122.1%
BASEALT					
<=2_ULN	3/14=21.43%	1/11=9.09%	12.34%	-15.06%	39.74%
2-5_ULN	25/52=48.08%	0/27=0.00%	48.08%	33.58%	62.58%
>5_ULN	9/16=56.25%	0/3=0.00%	56.25%	7.57%	104.9%
PCRCAT					
<8_LOG_IU/mL	25/34=73.53%	1/23=4.35%	69.18%	52.17%	86.19%
>=8_LOG_IU/mL	12/48=25.00%	0/18=0.00%	25.00%	10.59%	39.41%

TABLE 4.2 D

EAG_SEROCONVERSION_AT_WEEK_48

	ETV	PLACEBO	DIFF	LOWER	UPPER
ALL	22/82=26.83%	7/41=17.07%	9.76%	-5.23%	24.74%
REGION					
AMERICAS	9/30=30.00%	0/9=0.00%	30.00%	7.80%	52.20%
ASIA	6/18=33.33%	4/15=26.67%	6.67%	-24.56%	37.89%
EUROPE	7/34=20.59%	3/17=17.65%	2.94%	-19.71%	25.59%
METHOD					
Household	3/6=50.00%	0/1=0.00%	50.00%	-55.85%	155.9%
Mother/Child	14/50=28.00%	5/22=22.73%	5.27%	-16.21%	26.76%
Transfusion	1/5=20.00%	0/3=0.00%	20.00%	-34.84%	74.84%
Unknown	4/21=19.05%	2/15=13.33%	5.71%	-18.33%	29.76%
GENOTYPE					
A	6/15=40.00%	2/8=25.00%	15.00%	-23.92%	53.92%
B	1/7=14.29%	0/7=0.00%	14.29%	-17.90%	46.47%
C	9/23=39.13%	2/14=14.29%	24.84%	-2.24%	51.93%
D	4/31=12.90%	3/10=30.00%	-17.10%	-47.85%	13.66%
OTHER	2/6=33.33%	0/2=0.00%	33.33%	-37.55%	104.2%
BASEALT					
<=2_ULN	2/14=14.29%	2/11=18.18%	-3.90%	-33.15%	25.35%
2-5_ULN	13/52=25.00%	5/27=18.52%	6.48%	-12.31%	25.28%
>5_ULN	7/16=43.75%	0/3=0.00%	43.75%	-4.93%	92.43%
PCRCAT					
<8_LOG_IU/mL	16/34=47.06%	7/23=30.43%	16.62%	-8.58%	41.83%
>=8_LOG_IU/mL	6/48=12.50%	0/18=0.00%	12.50%	0.45%	24.55%

TABLE 4.2 E

ALT_NORMAL_AT_WEEK_48

	ETV	PLACEBO	DIFF	LOWER	UPPER
ALL	53/82=64.63%	10/41=24.39%	40.24%	23.51%	56.97%
REGION					
AMERICAS	17/30=56.67%	1/9=11.11%	45.56%	18.43%	72.69%
ASIA	17/18=94.44%	6/15=40.00%	54.44%	27.49%	81.40%
EUROPE	19/34=55.88%	3/17=17.65%	38.24%	13.60%	62.87%
METHOD					
Household	4/6=66.67%	0/1=0.00%	66.67%	-38.34%	171.7%
Mother/Child	34/50=68.00%	7/22=31.82%	36.18%	12.82%	59.55%
Transfusion	3/5=60.00%	0/3=0.00%	60.00%	-0.19%	120.2%
Unknown	12/21=57.14%	3/15=20.00%	37.14%	7.86%	66.43%
GENOTYPE					
A	10/15=66.67%	2/8=25.00%	41.67%	3.33%	80.00%
B	4/7=57.14%	2/7=28.57%	28.57%	-21.07%	78.21%
C	19/23=82.61%	3/14=21.43%	61.18%	34.69%	87.67%
D	16/31=51.61%	3/10=30.00%	21.61%	-11.80%	55.02%
OTHER	4/6=66.67%	0/2=0.00%	66.67%	-4.22%	137.5%
BASEALT					
<=2_ULN	7/14=50.00%	2/11=18.18%	31.82%	-2.90%	66.54%
2-5_ULN	35/52=67.31%	8/27=29.63%	37.68%	16.25%	59.11%
>5_ULN	11/16=68.75%	0/3=0.00%	68.75%	20.85%	116.6%
PCRCAT					
<8_LOG_IU/mL	28/34=82.35%	7/23=30.43%	51.92%	29.16%	74.67%
>=8_LOG_IU/mL	25/48=52.08%	3/18=16.67%	35.42%	13.14%	57.69%

5. Statistical Reviewer's Conclusions

Entecavir at .015 mg/kg has been confirmed to be a clinically effective treatment for the treatment of chronic hepatitis B in children aged 2 to 17 years. The pattern of efficacy already demonstrated in adults was confirmed in the randomized, controlled trial conducted in children. The ETV regimen was statistically significantly and clinically meaningfully more effective than placebo in suppressing viral load at week 48 and in inducing ALT normalization at the same time point. ETV was estimated to have slightly more than 40% success rates than placebo on both endpoints. With respect to E antigen sero-conversion, it was estimated to about 10% better than placebo but this estimate fell slightly short of statistical significance. This may, of course, be a consequence of the small sample size in the pediatric study. Results in adult studies suggest it is effective with respect to this endpoint as well.

The efficacy was estimated to be consistent across sex, race, age and other sub-groups with one exception. Children with genotype D infections had much lower success rates with respect to all three endpoints than did children with genotypes A, B, or C. A logistic regression of viral suppression rate on treatment, genotype, and baseline viral load suggested three conclusions. First and most important, ETV was estimated to be superior to placebo in all genotypes, as suggested by the graph in section 3.1.2 above. Second, there was an estimated interaction between genotype, baseline viral load, and treatment, as shown by the steeper decline of the curve for success rate for genotype D. Third, part of the observed lower success rate was due to the higher baseline viral load in genotype D, as conjectured by the applicant. The clinical reviewer has observed that higher baseline viral loads are in the general HBV population typically higher than with other genotypes. Nonetheless, baseline viral load and genotype are what they are; they are not treatment options. The choice of ETV for treatment even in this sub-group seems to be reasonable on the grounds of efficacy unless there was a substantial safety concern.

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Mathematical Statistician

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02/27/2014

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