CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-003/SE1-002

21-004/SE1-002

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#:	21-003/S-002
	21-004/S-002
APPLICANT:	GlaxoSmithKline
NAME OF DRUG:	Epivir-HBV® Tablets
	Epivir-HBV® Oral Solution
INDICATION:	Treatment of Hepatitis B Infection in Pediatric Patients
TYPE OF REVIEW:	Clinical
MEDICAL INPUT:	Barbara Styrt, M.D. (HFD-530), Melisse Baylor, M.D. (HFD-530)

STATISTICAL REVIEW AND EVALUATION

NDA#: 21-003, 21-004

1. Background

1.1 Objectives in Trials

The applicant submitted two pivotal randomized, double blind, controlled clinical trials with epivir-HBV, trial 2020 and trial 30903.

The primary objective of these studies was to assess the clinical and antiviral efficacy of epivir-HBV (EPV) in children infected with chronic hepatitis B.

1.2 Summary of Study Designs

1.2.1 Trial 2020:

This study was a small dose-ranging study of short duration. 52 subjects were randomized to one of five doses of epivir:

1) 0.35 mg/kg bid (8 subjects)
2) 3 mg/kg qd (11 subjects)
3) 1.5 mg/kg bid (10 subjects)
4) 4 mg/kg bid (11 subjects)
5) 100 mg qd (12 subjects).

The subjects received the assigned dose for 4 weeks and were followed up for a further 12 weeks. Only PK endpoints were recorded. The small sample size, short duration, and lack of clinical endpoints preclude a conventional statistical efficacy analysis of this trial. The FDA medical reviewer will discuss the PK aspects of this trial. The statistical review will not address this trial further.

1.2.2 Trial 30903:

This study was a double-blind, randomized, placebo-controlled two-arm, parallel, multi-center, multinational trial using children aged 2-18 infected with chronic hepatitis B.

Subjects were randomized to 52 weeks of either 3 mg/kg qd of EPV (as a 5 mg/mL oral solution) or placebo in a 2:1 ratio. Subjects with a mass > 33 kg received at most 100 mg of EPV, regardless of their mass. Randomization was unstratified.

1.3 Subject Accounting and Baseline Characteristics, Trial 30903

286 subjects were randomized to receive treatment. The treated population was 64% male with an age range of 1 to 17 years (median age 9 years). They were 70% white, 7% black, and 19% Asian. Mean HBV DNA level at baseline was 2058 MEq/mL; mean ALT was 2.9 * ULN (upper limit of normal); mean bilirubin was 0.4 * ULN.

Table 1.3 A summarizes the subject status in trial 30903.

TABLE 1.3 A
SUBJECT STATUS IN TRIAL 30930

	Placebo	EPIVIR
Randomized, Received Drug	95	191
Completed	91	185
Discontinued	4	6
Adverse event	1	1
Lost to follow-up	2	2
Other	1	3

1.4 Summary of Methods of Assessment

1.4.1 Schedule of Measurements

In trial 30903, HBV DNA was measured at baseline and at weeks 4, 8, 16, 24, 32, 40, 48, and 52, using the [redacted] assay with limit of quantitation (LOQ) [redacted] Hepatitis B e antigen (HBeAg) was measured at the same times using the [redacted] or the [redacted] assay.

1.4.2 Assessment of Treatment Effects

In trial 30903, the primary endpoint was percent BLQ on both HBV DNA and HBeAg assays at week 52. Secondary endpoints included persistence of BLQ status on each of HBV DNA and HBeAg separately and return of ALT to below upper limit of normal (ULN).

1.5 Summary of Statistical Analysis

In trial 30903, the primary endpoint of percent BLQ on both HBeAg and HBV DNA assays was analyzed using the chi-square test for difference in rates in a simple 2-by-2 table. An ITTI analysis was used: subjects were required to be positive with respect to HBsAg and HBeAg at baseline, or at the screening visit closest to baseline if baseline measurement was missing. Subjects with missing data at week 52 were counted as failures (not BLQ).

This endpoint was also analyzed by logistic regression, using baseline ALT, baseline HBV DNA, baseline Knodell HAI score, age, weight, and body mass index (BMI) = wt in kg/ht in meters as continuous covariates and cirrhosis, ethnic origin, and gender as categorical covariates.

2. Summary of Applicant's Results, Trial 30903:

There was a statistically significantly higher percentage of subjects with HBeAg and HBV DNA both BLQ on the Epivir arm than on the placebo arm. The applicant also looked at each of HBeAg and HBV DNA separately, at a three component endpoint = HBeAg and HBV DNA negative and HBeAb positive, and at subjects with ALT levels decreasing from > ULN at baseline to < ULN at week 52. The percent successful in each of these categories on each arm are given in table 2 A, together with p-values comparing the two arms for each endpoint.

TABLE 2 A
HBeAg, HBV DNA, ALT IN TRIAL 30903
Percent Successful

	Epivir	Placebo	P-value
HBeAg+HBV DNA BLQ	44/191 = 23%	12/95 = 13%	.037
HBeAg+HBV DNA BLQ and HBeAb +ve	42/191 = 22%	12/95 = 13%	.057
HBeAg BLQ	50/191 = 26%	14/95 = 15%	.029
HBV DNA BLQ	117/191 = 61%	15/95 = 16%	<.001
ALT < ULN	100/183 = 55%	11/88 = 13%	<.001

The applicant also used a logistic regression to examine possible interactions between treatment and various baseline covariates. They found no significant interactions with baseline ALT, race, or gender. They did find significant treatment interactions with baseline HBV DNA and age. Subjects with baseline HBV DNA < 800 MEq/mL had better response with placebo and hence the treatment difference between Epivir and placebo was smaller in that subgroup.

Responses rates by age category are given in table 2 B.

TABLE 2 B
HBeAg+HBV DNA -VE, BY AGE IN TRIAL 30903

	Percent Successful	
Age	Epivir	Placebo
2-6 yrs	16/49 = 33%	3/38 = 8%
7-12 yrs	20/95 = 21%	5/31 = 16%
13-17 yrs	8/47 = 17%	4/26 = 15%

Adolescents show both a higher response on placebo and a lower response on Epivir than do the younger age groups. This interaction was statistically significant at level .063. (Interactions are harder to detect than are main effects of treatment. In addition, the default assumption should be that interactions do exist and one should be trying to prove the null hypothesis of no interaction rather than to merely fail to reject it. Consequently, it is conventional to consider interactions as statistically significant if the p-value < .10 or even < .15). The applicant also fit a multivariate logistic regression including baseline ALT, baseline HBV DNA, baseline HAI score, age, and age-treatment interaction as covariates. In this regression, the age-treatment interaction was significant at level of .11 rather than .063. The applicant suggested that this confounding with other baseline covariates may explain the apparent age-treatment interaction.

3. Summary of Applicant's Conclusions

The applicant concluded that in children with chronic hepatitis B, 52 weeks of epivir treatment was significantly more effective than placebo in producing complete virologic response, as measured by viral DNA and e antigen. Epivir was also more successful than placebo at serum ALT normalization. The drug was well tolerated for 52 weeks of treatment.

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4. Statistical Reviewer's Comments and Analyses

The primary endpoint for the pediatric indication in trial 30903 is a surrogate marker for post-treatment biopsy results. The biopsy would be the gold standard for efficacy but it is unethical to collect such data in children. This raises a question as to whether the applicant's choice of surrogate marker is the best choice. This review will examine the following aspects: 1) sensitivity of the protocol primary endpoint to loss to follow-up, 2) treatment effects on other surrogate endpoints, 3) interactions between treatment and various baseline covariates, and 4) frequency of rebounds from BLQ to observable levels of HBV DNA and HBeAg.

4.1 Sensitivity of Primary Endpoint to Loss to Follow-Up

The protocol of trial 30903 specifically classifies a subject as a failure if they miss their week 52 visit. Using this definition, the percentages successful (= both HBeAg and HBV DNA BLQ) were as given in table 2 A above: 44/191 = 23% on epivir and 12/95 = 13% on placebo with a p-value of .037. However, there were three subjects classified as failures because they were lost to follow-up at week 52 but who might easily be considered successes if a slightly larger time window were used for the last visit. The complete record of HBeAg, HBV DNA, and ALT (raw and as a multiple of ULN) for these three subjects is given in table 4.1 A.

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

visits) rather than at day 365 and had a sequence of visits prior to the final one at which HBV DNA was BLQ [redacted], at which HBeAg was N(egative), and at which ALT had dropped to below or nearly below ULN. If these three subjects are all classified as successes then the percents successful on the two arms are as follows: 45/191 = 24% (instead of 44/191) on epivir and 14/95 = 15% (instead of 12/95) on placebo. The new p-value is .085 instead of .037.

This should not be interpreted simply as saying that statistical significance disappears under a small, plausible change in the interpretation of the data. A p-value of .037 is indeed less than the formal target value of .05 but it would be interpreted as good but not incontestable evidence of a real treatment effect. A p-value of .085 would be interpreted as not quite so good but still suggestive evidence of a real treatment effect.

In summary, there is suggestive to good evidence that there is a real treatment effect on the combined HBV DNA, HBeAg endpoint of modest effect: around a 9% improvement over placebo. The trial is underpowered to establish the reality of this modest effect completely convincingly. It also is considered by the medical reviewers that no more powerful study could be conducted in this population.

4.2 Treatment Effects on Other Surrogate Endpoints

The evidence supporting reality of the modest treatment effect discussed in section 4.1 can be strengthened by examining treatment effects on three individual surrogate markers: HBV DNA, HBeAg, and ALT. The results for these three endpoints are given in table 4.2 A. For HBV DNA and HBeAg, HEAL means BLQ, for ALT it means <= ULN. For convenience, the results for the primary endpoint and the sensitivity analysis on it are included in this table.

TABLE 4.2 A

PRIMARY & SECONDARY ENDPOINTS IN TRIAL 30903

	EPIVIR			PLACEBO			ODDS	95% LIMITS		
ENDPOINT	HEAL	FAIL	%HEAL	HEAL	FAIL	%HEAL	RATIO	LOWER	UPPER	P_VAL
HBV DNA	121	70	63%	17	78	18%	7.93	4.35	14.47	<.001
HBeAg	51	140	27%	17	78	18%	1.67	.90	3.09	.10
ALT	124	67	65%	22	73	23%	6.14	3.50	10.8	<.001
Primary	44	147	23%	12	83	13%	2.07	1.07	4.00	.037
Sens.	45	146	24%	14	81	15%	1.78	0.92	3.44	.085

One can see that Epivir has a statistically significant effect on both viral load and ALT: 45% more subjects with undetectable viral load and 42% more subjects with normal ALT levels at week 52. The effect on HBeAg is much smaller, 9% more subjects with undetectable HBeAg and it is problematic whether this observed effect is real or statistical noise (p-value = .10). The levels of E antigen are the main component keeping the primary endpoint low (9-10% improvement on placebo).

The overall impression is that two out of three possible surrogate markers for histologic change show a clear epivir superiority to placebo.

4.3 Interactions between Treatment and Baseline Covariates

It may be important to label any baseline covariates which suggest better or worse than average response to epivir. Table 4.3 A gives the success rates on both arms for the primary endpoint (including the three successes last observed on days 329-343) as sorted by region, race, gender, age, baseline ALT, baseline HBV DNA, and baseline Knodell score.

TABLE 4.3 A

PRIMARY ENDPOINT BY COVARIATES IN TRIAL 903

	EPIVIR			PLACEBO		
REGION	HEAL	FAIL	%HEAL	HEAL	FAIL	%HEAL
EEurope	18	38	32%	1	21	5%
NAmerica	14	43	25%	8	28	22%
WEurope	12	55	18%	4	26	13%
SAmerica	1	10	9%	1	6	14%
RACE						
Asian	10	23	30%	2	20	9%
White	30	109	22%	11	49	18%
Other	5	14	26%	1	12	8%
SEX						
F	18	50	26%	4	30	12%
M	27	96	22%	10	51	16%
AGE						
< 7	17	32	35%	3	35	8%
7-12	20	75	21%	6	25	19%
>=13	8	39	17%	5	21	19%
BASELINE ALT						
< 2 ULN	13	85	13%	4	36	10%
>= 2 ULN	32	61	34%	10	45	18%
BASELINE HBV DNA						
<800	31	65	32%	12	33	27%
800-4K	11	57	16%	2	34	6%
>=4K	3	24	11%	0	14	0%
BASELINE KNODELL SCORE						
0-4	21	82	20%	5	40	13%
5-9	20	33	38%	5	22	19%
10-13	2	5	29%	3	9	25%
WEIGHT IN KG						
< 33 Kg	28	72	28%	6	48	11%
>=33 Kg	17	74	19%	8	32	20%

There are a number of features that suggest treatment-covariate interactions. The treatment difference is larger in Eastern Europe than in North America, larger in Asians than in Whites, larger in the under 7 children than in adolescents. In all these cases, the epivir response went down and the placebo response went up in the group with the smaller treatment difference. Also the treatment difference was larger in sicker

subjects (baseline ALT >= 2 ULN, baseline HBV DNA >=4K Meq/mL, or baseline Knodell score 5-9). With respect to these three covariates, the change in response in each arm is less consistent. Both epivir and placebo give higher response in subjects with high baseline ALT and high baseline Knodell score but the epivir goes up more than the placebo response; both arms give poorer response with high baseline HBV DNA but the placebo goes down more than the epivir response. Finally, the difference between treatment arms disappeared in subjects weighing more than 33 kg. Since such subjects received only 100 mg of drug regardless of weight, it is suggestive a posteriori that these subjects were underdosed on active drug. That doesn't explain why the placebo cure rate goes up in this group. It should also be noted that 100 mg is the approved adult dose.

An immediate question prompted by table 4.3 A is which, if any, of the observed treatment-covariate interactions are statistically significant. The sponsor has suggested that some of the apparent interactions are due to confounding among the various baseline covariates. As shown in table A.1 in the appendix, there are a number of associations among the baseline covariates: East Europeans were younger than North Americans and were almost all boys; Asians were younger and more likely to be female than Whites; females were younger than males. The existence of these associations does not decide which apparent interactions are real and which are due to confounding with more important covariates.

The FDA reviewer addressed this question by fitting multivariate logistic regression models for the primary endpoint, using treatment, covariates, and treatment-covariate interaction terms as predictors. The results were slightly different from those reported by the applicant. Even after adjusting for baseline HBV DNA, baseline ALT, baseline bilirubin, and baseline Knodell score, three of the demographic covariates (age, race, and region) had statistically significant interactions with treatment. Gender had marginally significant results, depending on exactly how the other covariates were entered into the model. Recall from table 4.3 A that gender also had a smaller observed difference in treatment effect than did the other demographic covariates. The p-values for these covariate-treatment

interactions are given in table 4.3 B. (Recall that interactions are considered statistically significant if the p-value < .10.)

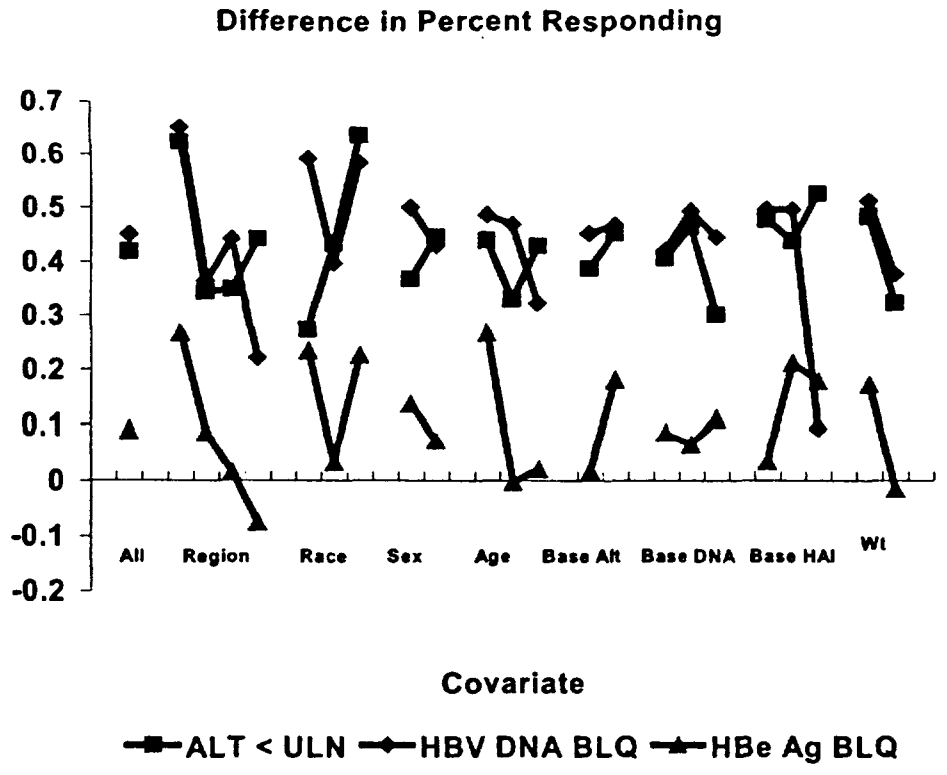
TABLE 4.3 B
TREATMENT-COVARIATE INTERACTIONS

COVARIATE	P-VALUE OF INTERACTION		
	Model A	B	C
Gender	.18	.13	.07
Age	.02	.03	.05
Race	.01	.02	.02
Region	.002	.003	.001

Model A assumed that both Knodell score and age had linear effects and interactions with treatment; models B and C assumed that the effects and interactions might be non-linear. Model C substituted baseline AST for baseline ALT since AST was mathematically, if not clinically, the better predictor of response in this data set. As an explanatory footnote, one should note that logarithms of baseline HBV DNA, baseline ALT, and baseline bilirubin were used in the multivariate logistic model.

Weight, categorized as above and below 33 Kg, was also tried in the above multivariate logistic models but was not found to be even marginally significant when other covariates were included.

The FDA statistical reviewer also examined the analogous tables for the three secondary endpoints of week 52 HBV DNA, week 52 HBeAg, and week 52 ALT. The pattern of apparent interactions are similar to those seen in table 4.3 A. The actual numbers are relegated to the appendices. A visual summary of the data which allows comparison of the similarities and differences in covariate interactions among the three endpoints is given in figure 4.3 A.



This figure shows three curves which plot the difference between epivir and placebo success rates on the three endpoints: HBV DNA BLQ, HbeAg BLQ, and ALT < ULN. The differences in rates are plotted for all subjects pooled, by region, race, sex, age, baseline ALT, baseline HBV DNA, baseline HAI score, and weight. The ordering of the categories is the same as in table 4.3 A. The single most noticeable feature of the plot is that epivir is superior to placebo on all three endpoints in all categories, except for HBeAg BLQ in South America (the region with the smallest sample size). It seems persuasive that none of the interactions manifested by the up and down movement of the lines representing treatment differences are large enough to warrant language in the label.

4.4 Rebounds of HBV DNA and HBeAg

The FDA reviewer also explored the frequency with which viral load and HBeAg reached BLQ and then rebounded. Rebounds were counted with and without confirmation. Rebounds without confirmation mean that there was at least one measurement > LOQ after at least one measurement BLQ. Confirmed rebounds occurred when there were two consecutive measuremenst > LOQ after at least two consecutive measurements that are BLQ. Both set of results are summarized in table 4.4 A with occurrence/non-occurrence of rebound cross-classified by status with respect to the final primary endpoint. Notice that subjects with a rebound and a success on the primary endpoint must have at least one >LOQ value between their first BLQ value and their final BLQ value at week 52. (The primary endpoint in this table is the last line of table 4.2 A above.)

TABLE 4.4 A

REBOUNDS FROM BLQ TO DETECTABLE

RELAPSES OF HBeAg		UNCONFIRMED		CONFIRMED	
Primary Endpt	HBeAg	EPIVIR	PLACEBO	EPIVIR	PLACEBO
Success	Stay BLQ				
Success	Rebound				
Success	BLQ Last Only				
Failed	Never BLQ				
Failed	Stay BLQ				
Failed	Rebound				

RELAPSES OF HBV DNA		UNCONFIRMED		CONFIRMED	
Primary Endpt	HBV DNA	EPIVIR	PLACEBO	EPIVIR	PLACEBO
Success	Stay BLQ				
Success	Rebound				
Failed	Never BLQ				
Failed	Stay BLQ				
Failed	Rebound				

In tables 4.4 B and 4.4 C, we give visit by visit listing for the three subjects whose HBV DNA had a confirmed BLQ followed by a confirmed Rebound followed by a success on the primary endpoint and for the three subjects whose e Antigen never had a confirmed BLQ but who had a success on the primary endpoint.

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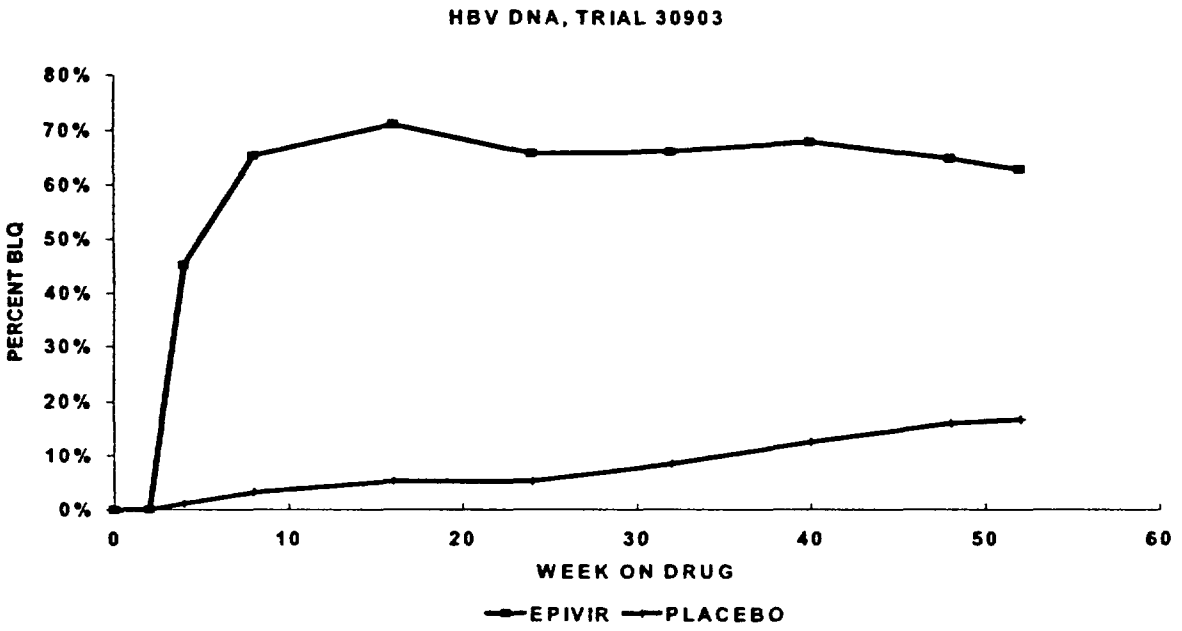
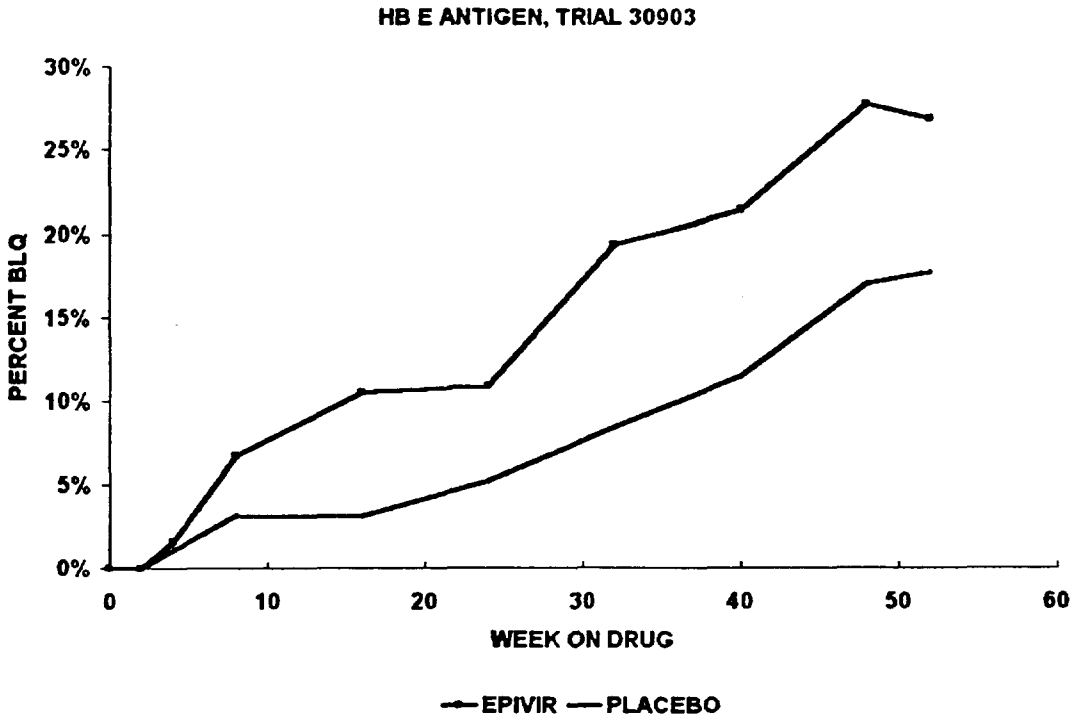
All three of the subjects in table 4.4 C appear to be clearly responsive on HBV DNA but have HBeAg that lingers until late in the study.





Figures 4.4 A and B show the percents of subjects who are BLQ on these two variables each week. These figures do not keep track of rebounds.

An overall impression from these tables and graphs is that there is a fair amount of up and down variation in HBV DNA over time on the epivir arm and that there is a slow, steadily increasing response on placebo. For both arms, there is less up and down variation in HBeAg, partly due to the fact that response on HBeAg takes longer.

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5. Statistical Reviewer's Summary

Given that epivir has already been demonstrated effective in treatment of hepatitis B in adults, based on histologic endpoints, there is satisfactory evidence of its efficacy in children for these disease as well. The effect is modest and of marginal statistical significance on HBeAg loss. The effect is larger and highly statistically significant on both reduction of HBV DNA to BLQ and on reduction of ALT to < ULN. The evidence from adult studies suggests that these endpoints have only modest correlation with histologic endpoints. Thus the magnitude of the treatment effect on histologic endpoints is difficult to predict.

There are statistically significant interactions with age, race, and geographic region. Asians, East Europeans, younger children all got a better response rate. The clinical relevance of these observations is difficult to determine.

Thomas Hammerstrom, Ph.D.
Mathematical Statistician

Concur: Dr. Soon

cc:
Archival NDA #21-003
Archival NDA #21-004

HFD-530
HFD-530/Dr. Birnkrant
HFD-530/Mr.
HFD-530/Dr. Kukich
HFD-530/Dr. Styrt
HFD-530/Dr. Baylor
HFD-725/Dr. Hammerstrom
HFD-725/Dr. Soon
HFD-725/Dr. Huque
HFD-725/Dr. Anello

APPENDIX

TABLE A.1
ASSOCIATIONS AMONG DEMOGRAPHIC COVARIATES

	RACE			AGE			SEX	
REGION	Asian	White	Other	>7	7-12	>=13	F	M
EEurope	0	78	0	25	34	19	7	71
NAmerica	35	43	15	36	40	17	46	47
WEurope	20	63	14	24	41	32	42	55
SAmerica	0	15	3	2	11	5	7	11

RACE	AGE			SEX	
	>7	7-12	>=13	F	M
Asian	21	22	12	37	18
White	61	86	52	55	144
Other	5	18	9	10	22

SEX	AGE		
	>7	7-12	>=13
F	39	42	21
M	48	84	52

TABLE A.2

WEEK 52 ALT< OR >ULN, BY COVARIATES

	EPIVIR			PLACEBO			ODDS
	<ULN	>ULN	%<ULN	<ULN	>ULN	%<ULN	RATIO
All	124	67	65%	22	73	23%	6.14
Region							
EEurope	40	16	71%	2	20	9%	25.00
NAmerica	37	20	65%	11	25	31%	4.20
WEurope	39	28	58%	7	23	23%	4.58
SAmerica	8	3	73%	2	5	29%	6.67
Race							
Asian	21	12	64%	8	14	36%	3.06
White	88	51	63%	12	48	20%	6.90
Other	15	4	79%	2	11	15%	20.63
Sex							
Female	43	25	63%	9	25	26%	4.78
Male	81	42	66%	13	48	21%	7.12
Age							
<7	28	21	57%	5	33	13%	8.80
7-12	65	30	68%	11	20	35%	3.94
>=13	31	16	66%	6	20	23%	6.46
Base ALT							
<2 ULN	60	38	61%	9	31	23%	5.44
>=2 ULN	64	29	69%	13	42	24%	7.13
Base HBV DNA							
<800	71	25	74%	15	30	33%	5.68
800-4K	41	27	60%	5	31	14%	9.41
>=4K	12	15	44%	2	12	14%	4.80
Base HAI							
0-4	74	39	65%	8	37	18%	8.78
5-9	35	18	66%	6	21	22%	6.81
10-13	6	1	86%	4	8	33%	12.00
Wt kg							
<33	65	35	65%	9	45	17%	9.29
>33	59	32	65%	13	27	33%	3.83

TABLE A.3

WEEK 52 HBV DNA < OR > LOQ

	EPIVIR			PLACEBO			ODDS
	BLQ	>LOQ	%BLQ	BLQ	>LOQ	%BLQ	RATIO
All	121		63%	17		18%	7.93
Region							
EEurope	39		70%	1		5%	48.18
NAmerica	35		61%	9		25%	4.77
WEurope	43		64%	6		20%	7.17
SAmerica	4		36%	1		14%	3.43
Race							
Asian	24		73%	3		14%	16.89
White	83		60%	12		20%	5.93
Other	14		74%	2		15%	15.40
Sex							
Female	44		65%	5		15%	10.63
Male	77		63%	12		20%	6.84
Age							
<7	29		59%	4		11%	12.33
7-12	66		69%	7		23%	7.80
>=13	26		55%	6		23%	4.13
Base ALT							
<2 ULN	59		60%	6		15%	8.57
>=2 ULN	62		67%	11		20%	8.00
Base HBV DNA							
<800	68		71%	13		29%	5.98
800-4K	41		60%	4		11%	12.15
>=4K	12		44%	0		0%	NA
Base HAI							
0-4	71		63%	6		13%	10.99
5-9	38		72%	6		22%	8.87
10-13	3		43%	4		33%	1.50
Wt kg							
<33	64		64%	7		13%	11.94
>33	57		63%	10		25%	5.03

TABLE A.4

WEEK 52 HBEAG < OR > LOQ

	EPIVIR			PLACEBO			ODDS
	BLQ	>LOQ	%BLQ	BLQ	>LOQ	%BLQ	RATIO
All	51		27%	17		18%	1.67
Region							
EEurope	20		36%	2		9%	5.56
NAmerica	17		31%	8		23%	1.55
WEurope	13		19%	5		18%	1.11
SAmerica	1		9%	1		17%	0.50
Race							
Asian	11		33%	2		10%	4.50
White	34		25%	13		22%	1.21
Other	6		32%	1		9%	4.62
Sex							
Female	19		28%	5		15%	2.30
Male	32		26%	11		19%	1.50
Age							
<7	18		38%	4		11%	4.95
7-12	23		25%	7		25%	0.99
>=13	10		21%	5		19%	1.14
Base ALT							
<2 ULN	14		14%	5		13%	1.17
>=2 ULN	37		40%	12		22%	2.37
Base HBV DNA							
<800	36		38%	13		29%	1.48
800-4K	12		18%	4		11%	1.71
>=4K	3		11%	0		0%	NA
Base HAI							
0-4	24		21%	8		18%	1.25
5-9	21		40%	5		19%	2.89
10-13	3		43%	3		25%	2.25
Wt kg							
<33	32		32%	8		15%	2.71
>33	19		21%	9		23%	0.91