

Without treatment (i.e., in placebo group), 60% of patients in Study 437 had no appreciable change in fibrosis, 19% had regression (improvement) of fibrosis and the other 21% had progression (worsening) of fibrosis. In those who received adefovir, however, a significantly greater proportion of patients, (41% in the adefovir 30 mg group and 34% in the 10 mg group) had regression of fibrosis compared with only 10% who experienced worsening fibrosis.

Similar results were also observed in Study 438, which enrolled e antigen-negative patients. In this study, however, the proportion of patients in the placebo group with worsening fibrosis at week 48, that is 36%, was higher than that seen in study 437. With adefovir treatment, only 4% progressed in fibrosis compared with 34% showing regression of fibrosis.

Also note that in Study 437, there was no statistically significant difference in the pattern of change in fibrosis in the adefovir 30 mg treated group versus the adefovir 10 mg group (p-value=0.3747).

This showed that adefovir 10 mg once daily was therapeutically beneficial in lessening the progression of fibrosis.

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2.4.2.2 Virologic Response in Studies 437, 438, 435 and 461—Efficacy

Changes in Serum HBV DNA

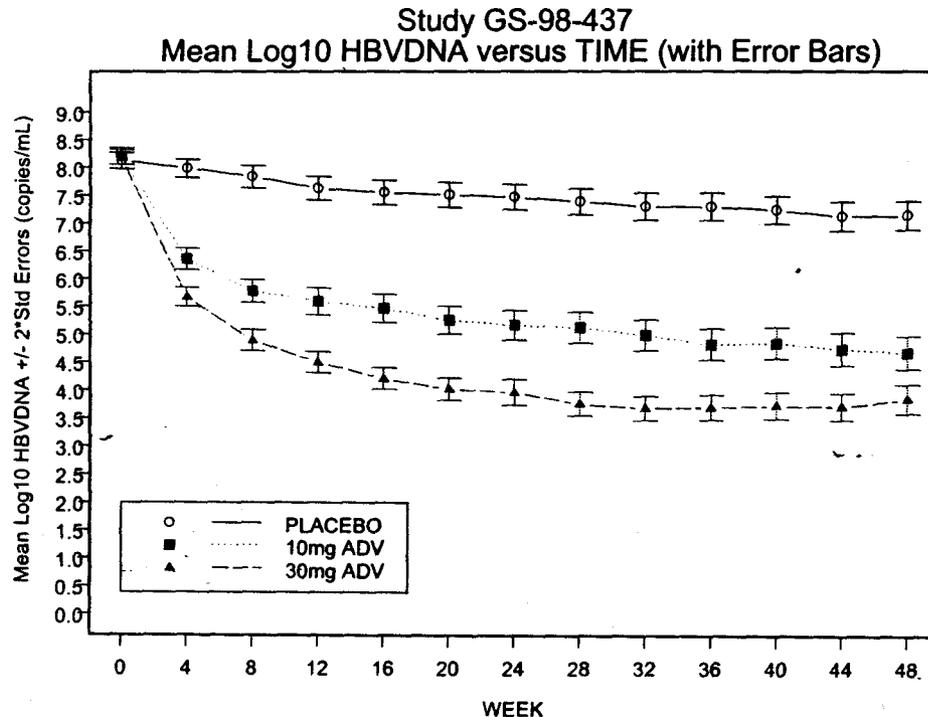
The virologic response in Studies 437 (HBeAg+), 438 (HBeAg-), 435 (Pre- or Post-OLT; lamivudine-resistant HBV), and 461 (lamivudine-resistant HBV) was measured by levels of serum HBV DNA using the Roche Amplicor PCR assay (lower limit of quantification=400 copies/mL).

First we will discuss the viral suppression as measured by serum HBV DNA through 48 weeks of therapy (and beyond when available) in Studies 437 and 438. Then we will discuss the same for Studies 435 and 461.

Figure 4 below shows the mean log₁₀ copies/mL of serum HBV DNA at each time point in Study 437 (HBeAg+ patients) through 48 weeks of treatment with either Placebo, ADV 10 mg once daily or ADV 30 mg once daily.

Figure 4:

Mean Serum HBV DNA levels (log₁₀ copies/mL) with Error Bars through First 48 Weeks—Study 437



This graph of mean log₁₀ HBV DNA over time shows that by Week 48, patients receiving

ADV 10 mg had approximately $3 \frac{1}{2} \log_{10}$ copies/mL suppression in HBV DNA, those patients receiving ADV 30 mg had approximately $4 \frac{1}{4} \log_{10}$ copies/mL suppression in HBV DNA. Also, see Table 8 for Week 48 results.

The differences between the ADV 30 mg and ADV 10 mg arm was statistically significant at every time point after Week 4. This indicates the ADV 30 mg was more effective in the suppression of HBV DNA than ADV 10 mg. Also, both adefovir doses had greater mean viral suppression relative to Placebo. Interestingly, patients receiving Placebo also had a mean reduction in serum HBV DNA of approximately $1 \log_{10}$ copies/mL.

The same results for ADV 10 mg and Placebo were confirmed in Study 438 where the mean change from baseline in serum HBV DNA at Week 48 was approximately $-3.5 \log_{10}$ copies/mL in the ADV 10 mg group and that for the Placebo group was $-1.23 \log_{10}$ copies/mL.

Statistical Reviewer's Comments:

In this NDA, the duration of antiviral therapy with adefovir for treatment of chronic hepatitis B was not established. In other words, there is no guidance as to when treatment with adefovir should end. We did additional analyses to see the effect of adefovir if additional 48 weeks of treatment is continued in the patients. This analysis is shown in Table 8.

In both, Studies 437 and 438, patients in each treatment group were re-randomized to receive either ADV 10 mg or Placebo in the second 48 weeks of treatment. This provided a basis for comparing whether stopping of treatment or continuation of treatment beyond 48 weeks provided any additional benefit.

As shown in Table 8, when patients receiving ADV 10 mg continued to receive ADV 10 mg in the second 48 weeks, there was additional suppression in serum HBV DNA. For example, at Week 72 (i.e., 24 additional weeks beyond Week 48), continuation of therapy on ADV 10 mg provided an additional median reduction of $-0.36 \log_{10}$ copies/mL. In comparison, in Study 438, for patients who continued on ADV 10 mg through 72 weeks of treatment, the viral suppression was maintained but no additional reduction in HBV DNA was observed.

However, when patients discontinued treatment with ADV 10 mg after Week 48 (i.e., received ADV 10 mg in first 48 weeks and Placebo in the second 48 weeks), a median increase of about $1.5 \log_{10}$ copies/mL was observed. The effect of discontinuation of therapy will be discussed in detail in Section 2.4.2.5.

Table 8:

Change from Week 48 in Serum HBV DNA (\log_{10} copies/mL)
 — during Second 48 weeks of treatment—Studies 437 and 438

	Study 437				Study 438		
	ADV 30 mg to Placebo	ADV 10 mg to Placebo	ADV 10 mg to ADV 10 mg	Placebo to ADV 10 mg	ADV 10 mg to ADV 10 mg	ADV 10 mg to Placebo	Placebo to ADV 10 mg
Week 48 †							
Mean ± SD	-4.38 ± 1.63	-3.52 ± 1.65		-0.99 ± 1.33	-3.54 ± 1.16		-1.23 ± 1.27
Median	-4.71	-3.38		-0.60	-3.83		-1.30
Q1, Q3	-5.47, -3.79	-4.82, -2.24		-1.71, -0.13	-4.38, -2.65		-2.03, -0.35
n	153	155		151	119		56
Week 52							
Mean ± SD	2.43 ± 1.56	1.84 ± 1.31	-0.03 ± 0.49	-1.71 ± 0.93	0.02 ± 0.47	1.96 ± 1.60	-1.75 ± 0.71
Median	2.47	1.79	0	-1.72	0	2.11	-1.81
Q1, Q3	1.26, 3.66	1.04, 2.92	-0.17, 0.10	-2.27, -1.24	0, 0	1.37, 2.87	-2.26, -1.29
n	126	64	77	129	76	38	56
Week 56							
Mean ± SD	3.12 ± 1.69	2.21 ± 1.26	-0.10 ± 0.53	-2.05 ± 0.99	-0.04 ± 0.33	2.59 ± 1.58	-2.08 ± 0.87
Median	3.08	2.21	-0.01	-1.96	0	2.45	-2.06
Q1, Q3	1.96, 4.53	1.50, 2.97	-0.33, 0.12	-2.77, -1.48	0, 0	2.05, 3.61	-2.69, -1.54
n	109	58	58	118	78	38	53
Week 60							
Mean ± SD	3.14 ± 1.95	1.99 ± 1.34	-0.30 ± 0.80	-2.31 ± 1.27	-0.05 ± 0.45	2.09 ± 1.59	-2.19 ± 1.10
Median	3.34	1.81	-0.20	-2.07	0	1.99	-2.26
Q1, Q3	1.61, 4.54	1.09, 3.13	-0.50, 0	-3.08, -1.53	-0.10, 0	1.08, 3.07	-2.73, -1.69
n	90	46	51	95	79	39	56
Week 64							
Mean ± SD	2.94 ± 1.99	1.79 ± 1.45	-0.27 ± 0.95	-2.43 ± 1.27	-0.10 ± 0.44	1.98 ± 1.58	-2.41 ± 1.03
Median	2.97	1.54	-0.15	-2.24	0	2.04	-2.43
Q1, Q3	1.15, 4.68	0.53, 1.54	-0.56, -0.15	-3.04, -1.73	-0.12, 0	0.64, 3.35	-3.10, -1.78
n	77	31	42	77	70	34	45
Week 68							
Mean ± SD	2.79 ± 2	2.15 ± 1.63	-0.14 ± 0.77	-2.60 ± 1.27	-0.01 ± 0.75	2.17 ± 1.84	-2.55 ± 0.92
Median	2.77	2.09	-0.19	-2.48	0	2.34	-2.61
Q1, Q3	0.90, 4.68	0.71, 3.12	-0.46, 0	-3.32, -1.90	-0.04, 0	0.57, 3.67	-3.11, -1.95
n	59	25	37	62	54	24	35

	Study 437				Study 438		
	ADV 30 mg to Placebo	ADV 10 mg to Placebo	ADV 10 mg to ADV 10 mg	Placebo to ADV 10 mg	ADV 10 mg to ADV 10 mg	ADV 10 mg to Placebo	Placebo to ADV 10 mg
Week 72							
Mean ± SD	2.70 ± 1.95	1.85 ± 1.6	-0.43 ± 0.62	-2.82 ± 1.22	-0.12 ± 0.63	2.07 ± 1.83	-2.59 ± 1.02
Median	3.03	1.38	-0.36	-2.60	0	1.59	-2.69
Q1, Q3	1.06, 4.31	0.31, 3.15	-0.78, 0	-3.73, -2.06	-0.13, 0	0.55, 3.80	-3.24, -1.86
n	47	20	28	47	36	17	25
Week 76							
Mean ± SD	3.10 ± 1.90	1.61 ± 1.31	-0.60 ± 0.76	-2.81 ± 1.31	-0.19 ± 0.54	2.22 ± 1.93	-2.37 ± 0.73
Median	3.66	1.31	-0.48	-2.57	0	2.04	-2.34
Q1, Q3	1.29, 4.68	0, 2.95	-0.81, -0.1	-3.77, -2.04	-0.29, 0	0.64, 3.73	-2.80, -1.80
n	36	15	20	34	23	10	16
Week 80							
Mean ± SD	3.64 ± 2	1.47 ± 1.33	-0.38 ± 0.71	-2.66 ± 1.57	-0.12 ± 0.31	2.36 ± 1.72	-2.17 ± 0.49
Median	4.65	1.25	-0.38	-2.75	0	2.59	-2.26
Q1, Q3	2.56, 4.99	0, 2.74	-0.65, 0.11	-3.85, -1.66	-0.20, 0	1.14, 3.67	-2.42, -1.88
n	25	12	15	20	20	8	9
Week 84							
Mean ± SD	3.36 ± 2.51	1.29 ± 1.35	-0.27 ± 0.85	-2.77 ± 1.53	0	3.73	-2.28 ± 0.58
Median	4.02	1.38	-0.57	-2.90	0	3.73	-2.28
Q1, Q3	1.54, 5.31	0, 2.67	-0.66, 0.53	-3.90, -1.40	0, 0	3.73, 3.73	-2.69, -1.87
n	14	11	9	10	1	1	2

HBV DNA = Hepatitis B Virus Deoxyribonucleic Acid

Q1 = 1st quartile, i.e., 25th percentile; Q3 = 3rd quartile, i.e., 75th percentile.

NOTE: In Study 437, the As-Treated population was used to compute the changes in serum HBV DNA levels for the second 48 weeks, because as the Applicant acknowledged in the NDA, there was a randomization dosing error that occurred in the second 48 weeks where 416 out of 459 patients who entered the second 48 weeks of the study received at least one incorrect bottle of the drug.

In Study 438, there was no such error. Therefore the results are based on the ITT population in the second 48 weeks.

† At Week 48, the change in serum HBV DNA is the change from Baseline (Week 0) as compared with Week 48.

Sources: FDA Statistical Reviewer's Analyses

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Table 9:
 Change from Baseline in Serum HBV DNA (log₁₀ copies/mL) at Week 48—
 Studies 435 and 461

	Study 435		Study 461		
	Cohort A (Post-Liver Transplant)	Cohort B (Waitlisted for Liver Transplant)	ADV 10 mg + LAM 100 mg	ADV 10 mg daily	LAM 100 mg daily
Baseline					
Mean ± SD	7.73 ± 1.63	7.06 ± 1.53	7.76 ± 0.79	8.38 ± 0.52	8.09 ± 0.69
Median	8.18	7.37	7.94	8.42	8.20
Q1, Q3	7.42, 8.79	6.59, 8.07	7.20, 8.29	7.97, 8.83	7.73, 8.57
n	180	119	20	19	19
Change in log₁₀ HBV DNA					
Week 4					
Mean ± SD	-1.97 ± 0.94	-2.26 ± 1.18	-1.76 ± 0.59	-1.89 ± 0.71	0.05 ± 0.27
Median	-2.08	-2.24	-1.90	-1.81	0.05
Q1, Q3	-2.57, -1.44	-2.80, -1.58	-2.20, -1.39	-2.15, -1.27	-0.18, 0.25
n	168	112	20	19	19
Week 12					
Mean ± SD	-3.04 ± 1.33	-3.02 ± 1.41	-2.71 ± 0.58	-2.88 ± 0.86	-0.17 ± 0.49
Median	-3.04	-2.96	-2.71	-2.55	-0.11
Q1, Q3	-3.68, -2.45	-4.19, -2.16	-2.95, -2.51	-3.28, -2.38	-0.40, 0.24
n	152	95	18	18	19
Week 16					
Mean ± SD			-2.95 ± 0.64	-3.11 ± 0.94	-0.00 ± 0.28
Median			-2.87	-2.86	-0.00
Q1, Q3			-3.24, -2.59	-3.63, -2.44	-0.15, 0.15
n	NA	NA	20	19	17
Week 24					
Mean ± SD	-3.76 ± 1.29	-3.39 ± 1.55	-3.51 ± 1.15	-3.51 ± 1.17	-0.02 ± 0.47
Median	-3.67	-3.67	-3.31	-2.95	0.06
Q1, Q3	-4.69, -3.03	-4.41, -2.73	-4.34, -2.66	-4.63, -2.54	-0.22, 0.29
n	124	60	11	12	11
Week 48					
Mean ± SD	-4.14 ± 1.54	-3.19 ± 1.86			
Median	-4.32	-4			
Q1, Q3	-5.12, -3.14	-4.37, -2.33			
n	61	17			
Week 60					
Mean ± SD	-4.31 ± 1.67	-4.15 ± 0.97			
Median	-4.70	-4.35			
Q1, Q3	-5.46, -3.36	-4.81, -4			
n	46	6			
Week 72					
Mean ± SD	-3.92 ± 1.90	-4.17 ± 0.34			
Median	-4.42	-4.17			
Q1, Q3	-5.31, -2.85	-4.41, -3.93			
n	30	2			

NA= Insufficient data

Source: FDA Statistical Reviewer's analysis based on Safety Update data.

Among the patients with lamivudine-resistant HBV in Studies 435 and 461, significant reduction in the serum HBV DNA was also seen upon treatment with ADV 10 mg (see Table 9). At Week 48, Cohorts A (post-liver transplant) and B (waitlisted for liver transplant) had a median reduction from baseline of approximately 4 log₁₀ copies/mL. In Study 461, the endpoint for virologic response was evaluated at Week 16 when a mean reduction from baseline of 2.86 log₁₀ copies/mL was observed with ADV 10 mg treatment. The median change from baseline in the monotherapy arm (ADV 10 mg) and the dual therapy arm (ADV 10 mg + LAM 100 mg) were similar, and had statistically significantly greater reduction in HBV DNA than the group treated with LAM 100 mg alone.

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2.4.2.3 Biochemical Response (Serum ALT) in Studies 437, 438 and 435—Efficacy

Table 10 shows the change from baseline in serum ALT (IU/L) through 72 weeks of treatment in Studies 437 and 438.

Table 10:

Change from Baseline in Serum ALT (IU/L)
 through 72 weeks—Studies 437 and 438

	Treatment Groups in First 48 Weeks						
	Study 437			Study 438			
	ADV 30 mg	ADV 10 mg	Placebo	ADV 10 mg	Placebo		
Baseline ALT							
Mean ± SD	123.8 ± 96.3	138.8 ± 153.6	138.9 ± 131.2	143.48 ± 125.31	149.85 ± 195.15		
Median	92	95	94	93	100		
n	173	171	167	123	61		
Change in ALT							
Week 24							
Mean ± SD	-66.2 ± 111.2	-78.9 ± 169.7	-20.5 ± 136.9	-103.37 ± 128.91	-67.46 ± 224.86		
Median	-37	-38	-7	-58	-33		
n	159	158	157	117	57		
Week 48							
Mean ± SD	-74.4 ± 128.4	-92 ± 167.2	-23 ± 140.7	-100.31 ± 123.13	-76.95 ± 213.5		
Median	-53.5	-50.5	-17	-55	-38		
n	144	152	148	118	55		
Change from Week 48 in ALT at	Treatment Groups in Second 48 Weeks						
	Study 437				Study 438		
	ADV 30 mg to Placebo	ADV 10 mg to Placebo	ADV 10 mg to ADV 10 mg	Placebo to ADV 10 mg	ADV 10 mg to Placebo	ADV 10 mg to ADV 10 mg	Placebo to ADV 10 mg
Week 72							
Mean ± SD	38.2 ± 68.9	99.7 ± 189.9	-19 ± 43.7	-79.4 ± 130.9	55.4 ± 72.6	3.0 ± 18.1	-45.6 ± 67.4
Median	14	6	-3	-33	38	0	-23
n	51	19	29	45	25	50	36

ALT = Alanine aminotransferase.
 IU/L = International units per liter. Units for measuring ALT.
 Q1 = 1st quartile, i.e., 25th percentile; Q3 = 3rd quartile, i.e., 75th percentile.

Source: For Study 437; Supporting Table for Figure 12C.2 (ITT population Year 1), Page 204 in Volume 217, and Supporting Table for Figure 8B.3 (AT population at Year 2), Page 210 in Volume 218. For Study 438; Supporting Table for Figure 12C.2 (ITT population Year 1), Page 277 in Volume 250, and Supporting Table for Figure 8B.2 (ITT population at Year 2), Page 98 in Volume 251.

As shown in Table 10 above, Figure 7 and Figure 8 on the changes in serum ALT over time, treatment with either ADV 10 mg (in Studies 437 and 438) or ADV 30 mg in Study 437 resulted in significant reduction in ALT through 72 weeks.

The proportion of patients who had normalized ALT by Week 48 were statistically significantly greater in the adefovir (30 mg or 10 mg) groups as compared with those receiving Placebo. ALT normalization was defined as ALT level \leq Upper Limit Normal (ULN) at the last non-missing ALT measurement.

Statistical Reviewer's Comments:

One approach to estimate the proportion of patients with ALT normalization at a given time point (or any other defined event for that matter) is to obtain a crude proportion by counting the number of patients who had ALT normalization at that time point and divide that by the total number of patients that we began with (e.g, $93/173 = 54\%$).

Another approach to estimate the proportion is to do a time-to-event type survival analysis using methods such as Kaplan-Meier analysis. With this approach, we would also account for patients who are censored between time point 0 and the future time points that are evaluated. For example, a proportion is computed at the end of every interval that will take into account patients who have not yet had a chance to have ALT normalization and are censored in that interval (such as loss-to-follow patients, etc.). Therefore, a Kaplan-Meier analysis approach will give better estimates of the proportions as it accounts for time and censoring.

Using the first approach we get the following results on proportion of patients with ALT normalization at Week 48. In Study 437, the proportion of patients with normalized ALT in the ADV 30 mg group was 93/173 (54%), in the ADV 10 mg group was 81/171 (47%) and in the Placebo group was 26/167 (16%) (Source: Table 32, Volume 216). In Study 438, the proportion of patients with normalized ALT in the ADV 10 mg group was 84/123 (68%) and in the Placebo group was 17/61 (28%). In this analysis, missing ALT data was treated as failure.

Using the Kaplan-Meier analysis we present the proportion of patients with ALT normalization at Week 48 in for Table 11 Study 437 and Table 12 for Study 438. Furthermore, in Section 2.4.2.5 we evaluate the additional proportion of patients who had ALT normalization in Year 2 if treatment is continued up to 72 weeks—for those patients who did not have ALT normalization in Year 1 at Week 48 (See Table 14 for Study 437 and Table 15 for Study 438).

Table 11:

Kaplan-Meier Analysis on Time to Onset of Normalization of ALT for Year 1
 (ITT Population with ALT > ULN at Baseline)
 —Study 437

Time Interval	Treatment Group					
	ADV 30 mg		ADV 10 mg		Placebo	
	At Risk	Cumulative Events (%)	At Risk	Cumulative Events (%)	At Risk	Cumulative Events (%)
Baseline (Week 0)	167	0 (0%)	167	0 (0%)	164	0 (0%)
>Baseline-Week 4	167	4 (2%)	167	3 (2%)	164	2 (1%)
>Week 4-Week 8	163	13 (8%)	164	12 (7%)	161	4 (2%)
>Week 8-Week 12	153	32 (19%)	155	21 (13%)	158	8 (5%)
>Week 12-Week 16	133	51 (31%)	146	42 (25%)	153	14 (9%)
>Week 16-Week 20	114	63 (38%)	125	60 (36%)	147	17 (11%)
>Week 20-Week 24	102	74 (45%)	107	64 (38%)	142	23 (14%)
>Week 24-Week 28	91	80 (48%)	103	81 (49%)	136	24 (17%)
>Week 28-Week 32	83	88 (53%)	84	82 (49%)	133	25 (16%)
>Week 32-Week 36	75	99 (60%)	82	90 (54%)	132	29 (18%)
>Week 36-Week 40	64	107 (65%)	74	94 (57%)	128	32 (20%)
>Week 40-Week 44	56	109 (67%)	70	102 (62%)	125	36 (23%)
>Week 44-Week 48	48	116 (72%)	60	106 (64%)	119	38 (24%)
95% CI at Week 48	(64.7%, 78.9%)		(56.9%, 71.7%)		(17.4%, 30.8%)	
p-value (ADV 10 mg vs Placebo) †			<0.001*			

† p-value is based on log-rank test.
 * p-value is statistically significant at 0.05 level of significance.
 NOTE: 1) ALT normalization is defined as ALT ≤ ULN at the post-baseline time point for patients with ALT > ULN at baseline.
 2) Normalization of ALT is referred to as an event. Cumulative event column shows the number and percentage of patients with normalization of ALT at the end of that interval.
 3) Number of patients at risk is at the beginning of an interval. Cumulative events and KM% (95% CI) are at the end of the interval.

Source: Supporting table for Figure 8 on Page 95 of Volume 217 of Study 437 Clinical Study Report.

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Table 12:

Kaplan-Meier Analysis on Time to Onset of Normalization of ALT for Year 1
 (ITT Population with ALT > ULN at Baseline)
 —Study 438

Time Interval	Treatment Group			
	ADV 10 mg		Placebo	
	At Risk	Cumulative Events (%)	At Risk	Cumulative Events (%)
Baseline (Week 0)	116	0 (0%)	59	0 (0%)
>Baseline-Week 4	116	7 (6%)	59	2 (3%)
>Week 4-Week 8	109	25 (22%)	57	9 (15%)
>Week 8-Week 12	91	46 (40%)	50	13 (22%)
>Week 12-Week 16	70	62 (53%)	46	16 (27%)
>Week 16-Week 20	54	67 (58%)	43	18 (31%)
>Week 20-Week 24	48	78 (68%)	41	20 (34%)
>Week 24-Week 28	37	82 (71%)	39	23 (39%)
>Week 28-Week 32	33	85 (74%)	35	23 (39%)
>Week 32-Week 36	30	86 (75%)	35	25 (43%)
>Week 36-Week 40	29	88 (76%)	33	26 (44%)
>Week 40-Week 44	27	89 (77%)	32	26 (44%)
>Week 44-Week 48	26	89 (77%)	31	26 (44%)
95% CI at Week 48	(69.4%, 84.8%)		(31.6%, 57.0%)	
p-value (ADV 10 mg vs Placebo) †	<0.001*			
† p-value is based on log-rank test. * p-value is statistically significant at 0.05 level of significance. NOTE: 1) ALT normalization is defined as ALT ≤ ULN at the post-baseline time point for patients with ALT > ULN at baseline. 2) Normalization of ALT is referred to as an event. Cumulative event column shows the number and percentage of patients with normalization of ALT at the end of that interval. 3) Number of patients at risk is at the beginning of an interval. Cumulative events and KM% (95% CI) are at the end of the interval.				

Source: Supporting table for Figure 8 on Page 250 of Volume 213 of Study 438 Clinical Study Report.

At Week 48, the proportion of patients with ALT normalization was statistically significantly higher in those treated with adefovir 10 mg relative to Placebo. In Study 437, the estimated proportion of patients with ALT normalization at Week 48 was 64% for ADV 10 mg versus 24% for Placebo with 95% CIs of (56.9%, 71.7%) for ADV 10 mg and (17.4%, 30.8%) for Placebo. In Study 438 the rates were 77% for ADV 10 mg (95% CI of [69.4%, 84.8%]) versus 44% for Placebo (95% CI of [31.6%, 57.0%]).

In Section 2.4.2.5 we discuss the effect of continuation of treatment in Year 2 on ALT normalization rates.

2.4.2.4 Serologic Response (HBeAg Seroconversion) in Study 437

Since Study 437 enrolled patients who were tested positive for the HBe antigen (HBeAg), one of the secondary efficacy endpoints was serologic response with respect to HBeAg. Serologic response was defined as the loss of HBeAg and concurrent gain of HBeAb at Week 48. Recall that Study 438 enrolled patient who were tested negative for HBeAg at baseline and as such serologic response cannot be determined.

Table 13 below shows the Kaplan-Meier estimates on the time-to-onset of HBeAg seroconversion for the first 48 weeks of therapy in Study 437.

Table 13:
 Kaplan-Meier Analysis on Time to Onset of HBeAg Seroconversion for Year 1
 (ITT Population with Positive Baseline HBeAg)
 —Study 437

Time	Treatment Group					
	ADV 30 mg		ADV 10 mg		Placebo	
	At Risk	Cumulative Events (%)	At Risk	Cumulative Events (%)	At Risk	Cumulative Events (%)
Baseline (Week 0)	163	0 (0%)	170	0 (%)	161	0 (0%)
>Baseline-Week 4	163	1 (1%)	170	1 (1%)	161	0 (0%)
>Week 4-Week 8	162	9 (6%)	169	4 (2%)	160	0 (0%)
>Week 8-Week 12	153	13 (8%)	166	6 (4%)	159	1 (1%)
>Week 12-Week 16	148	16 (10%)	164	7 (4%)	157	4 (3%)
>Week 16-Week 20	144	17 (10%)	163	9 (5%)	154	4 (3%)
>Week 20-Week 24	142	17 (10%)	161	13 (8%)	152	4 (3%)
>Week 24-Week 28	142	18 (11%)	157	15 (9%)	151	5 (3%)
>Week 28-Week 32	140	18 (11%)	153	16 (9%)	149	7 (4%)
>Week 32-Week 36	139	20 (12%)	150	18 (11%)	147	11 (7%)
>Week 36-Week 40	137	22 (14%)	148	20 (12%)	143	12 (8%)
>Week 40-Week 44	134	22 (14%)	145	22 (13%)	142	13 (8%)
>Week 44-Week 48	127	26 (17%)	139	23 (14%)	138	14 (9%)
95% CI at Week 48	(10.9%, 22.7%)		(8.5%, 18.9%)		(4.6%, 14.0%)	
p-value (ADV 10 mg vs Placebo) †			0.0726			

† p-value is based on log-rank test.

Source: Supporting table for Figure 4 on Page 31 of Volume 217 of Study 437 Clinical Study Report.

As seen here, based on Kaplan-Meier analysis, the estimated percentage of patients who seroconvert at Week 48 are 17% in the ADV 30 mg group, 14% in the ADV 10 mg group and 9% in the Placebo group. The differences in the estimated rates are only marginally significant.

In Section 2.4.2.5 we will investigate how many additional proportion of patients

seroconvert in the second 48 weeks of treatment (Year 2) if they did not convert in the first 48 weeks (Year 1).

2.4.2.5 Effect of Discontinuation of Therapy on Virologic, Biochemical, and Serologic Responses—Studies 437 and 438

Since the length of therapy for chronic hepatitis B has not been established, it is of interest to know what happens to the virologic response, i.e., serum HBV DNA levels, and the biochemical response, i.e., serum ALT when patients either continue treatment beyond 48 weeks or discontinue treatment.

In the following figures, we address the issue of the effect of discontinuation of treatment on serum HBV DNA and serum ALT levels

Figure 5:

Mean Serum HBV DNA levels (log₁₀ copies/mL) over time in Study 437

Left panel: patients with dose randomization errors in second 48 weeks included.

Right panel: patients with as-treated data in second 48 weeks shown.

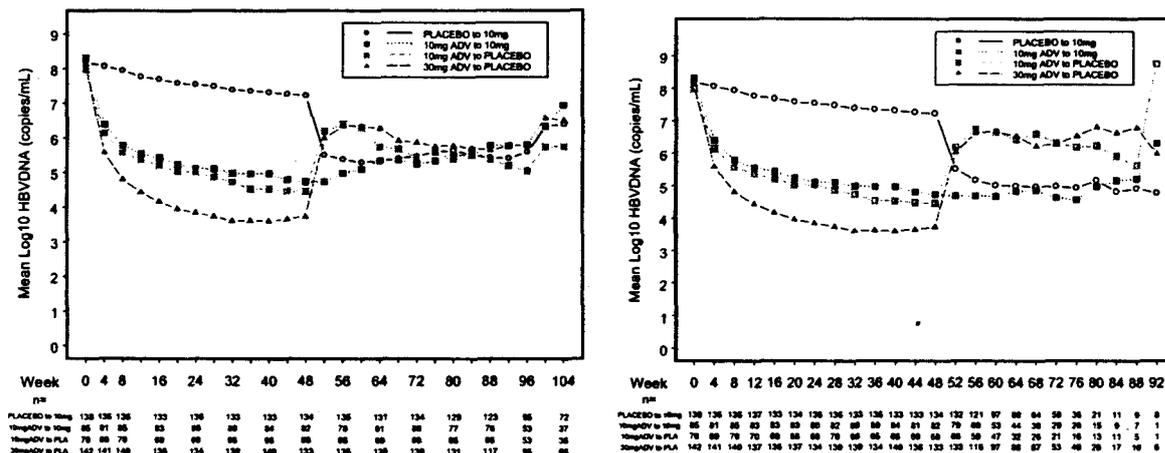


Figure 5 shows the serum HBV DNA levels through 48 weeks and all available data beyond 48 weeks for Study 437. In the left panel is the shown the data for all the ITT population. Recall that in the second 48 weeks, the Applicant acknowledged of a dose randomization error where patients received incorrect medication of either ADV 10 mg or Placebo. The data beyond 48 week shows that the mean log₁₀ HBV DNA bounce around for all groups. Due to the study medication dosing errors, this data is difficult to interpret.

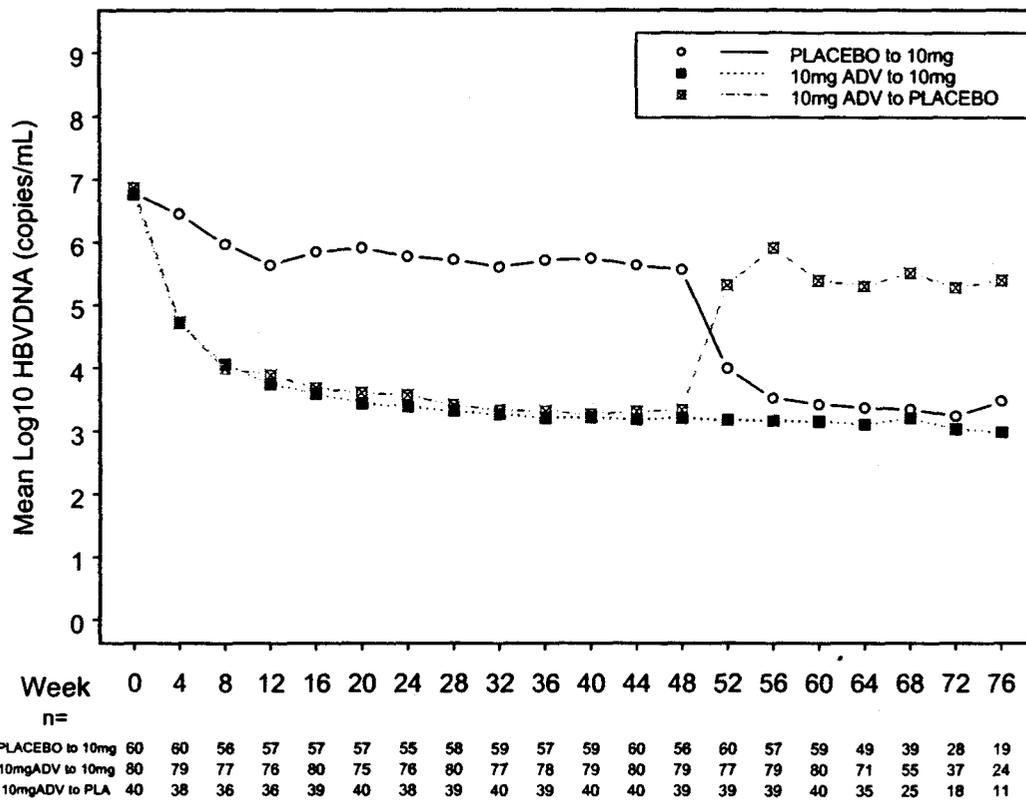
In the right panel we used data on ITT population through the first 48 weeks and data on

as-treated population in the second 48 weeks. In this graph, a salient point is that when patients were switched from adefovir treatment to placebo, serum HBV DNA levels promptly returned to levels closer to baseline within 4 to 8 weeks.

The same conclusion is reached for Study 438 based on data through 76 weeks shown in Figure 6.

Figure 6:

Mean Serum HBV DNA levels (log₁₀ copies/mL) through 76 Weeks in Study 438



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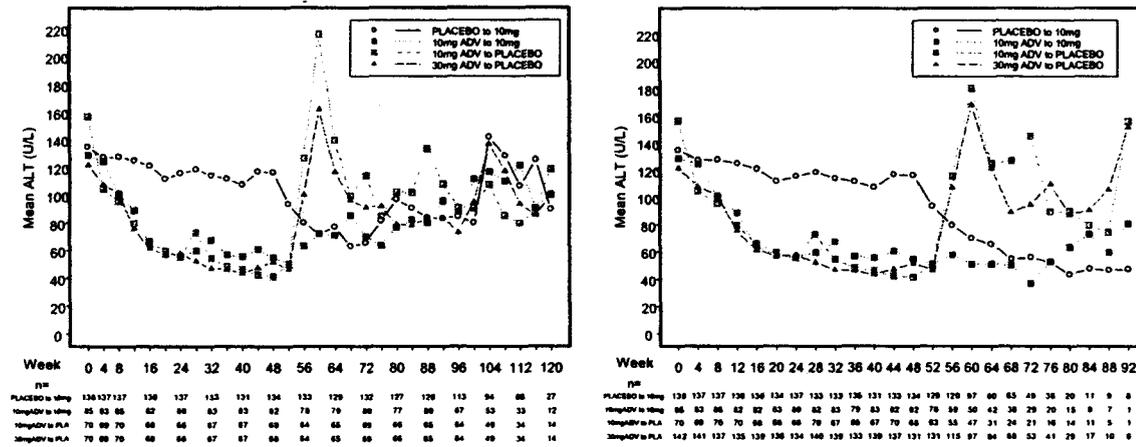
Figure 7 and Figure 8 show plots of serum ALT through 48 weeks and beyond in Studies 437 and 438.

Figure 7:

Mean Serum ALT (IU/L) over time in Study 437

Left panel: patients with dose randomization errors in second 48 weeks included.

Right panel: patients with as-treated data in second 48 weeks shown.



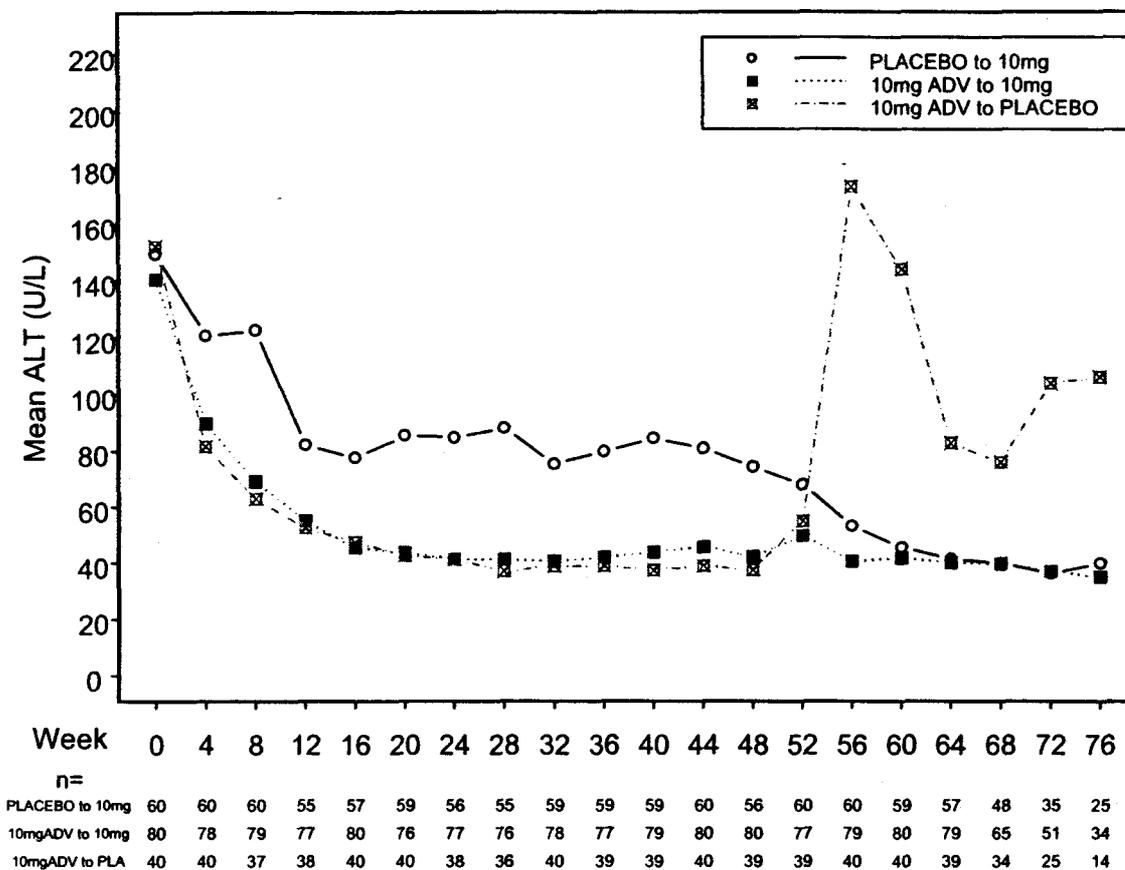
In Study 437, there was little separation between the curves for Adefovir 30mg group (which is in blue triangles) and Adefovir 10mg group (which is in red and orange squares) in the first 48 weeks.

Interestingly, patients in the Placebo group also experienced improvement in serum ALT over time in Study 437. Serum ALT levels peaked within 12 weeks (2-3 months) (which may be hepatic flares) when patients discontinued adefovir treatment, i.e., switched to placebo. Due to study medication dosing errors, data may be uninterpretable during the latter part of the second 48 week period (as shown in the left panel). However, the right panel shows the clear trends in ALT for second 48 weeks when patient data was analyzed as-treated.

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Figure 8:

Mean Serum ALT (IU/L) through 76 Weeks in Study 438



The improvement in serum ALT was more pronounced in Study 438 in the Placebo group. We do not have a good explanation of this phenomenon. It could potentially be due to the naturally fluctuating disease course observed in HBeAg negative patients. Perhaps it could be that these patients were more symptomatic as indicated by the high serum ALT at baseline, and hence, they were easily identifiable for enrollment.

A similar phenomenon of mean ALT levels going back to baseline upon discontinuation of adefovir treatment was observed in Study 438 because some patients experienced exacerbation of hepatitis (defined as ALT $\geq 10 \times$ ULN) upon discontinuation of adefovir.

Table 14 and Table 15 show the Kaplan-Meier analysis on time-to-onset of ALT normalization in Year 2 among those patients who did not have normalized ALT until Week 48 in both studies.

These analyses evaluate the effect of either continuation of treatment with adefovir 10 mg

through 72 weeks or discontinuation of treatment after 48 weeks.

Table 14:
 Kaplan-Meier Analysis on Time to Onset of Normalization of ALT for Year 2
 (As-Treated Population with ALT > ULN at Week 48)
 —Study 437

Time	Treatment Group							
	ADV 30 mg to Placebo		ADV 10 mg to Placebo		ADV 10 mg to ADV 10 mg		Placebo to ADV 10 mg	
	At Risk	Cum. Events (%)	At Risk	Cum. Events (%)	At Risk	Cum. Events (%)	At Risk	Cum. Events (%)
Week 48	49	0 (0%)	26	0 (0%)	41	0 (0%)	115	0 (0%)
>Week 48-Week 52	49	5 (10%)	26	1 (4%)	41	6 (15%)	115	5 (4%)
>Week 52-Week 56	43	6 (13%)	22	2 (9%)	32	10 (26%)	106	14 (14%)
>Week 56-Week 60	34	6 (13%)	19	2 (9%)	27	11 (29%)	80	19 (19%)
>Week 60-Week 64	26	6 (13%)	16	2 (9%)	22	11 (29%)	66	25 (27%)
>Week 64-Week 68	22	8 (21%)	11	2 (9%)	18	12 (33%)	50	30 (34%)
>Week 68-Week 72	16	8 (21%)	10	2 (9%)	13	13 (38%)	41	37 (47%)
95% CI at Week 48	(7%, 35.8%)		(0%, 20.3%)		(20.7%, 55.9%)		(35.1%, 58.9%)	
p-value (ADV 10 mg to ADV 10 mg vs ADV 10 mg to Placebo) †	0.0208*							

† p-value is based on log-rank test.
 * p-value is statistically significant at 0.05 level of significance.
 NOTE: 1) ALT normalization is defined as ALT ≤ ULN at the post-baseline time point for patients with ALT > ULN at baseline.
 2) Normalization of ALT is referred to as an event. Cumulative event column shows the number and percentage of patients with normalization of ALT at the end of that interval.
 3) Number of patients at risk is at the beginning of an interval. Cumulative events and KM% (95% CI) are at the end of the interval.

Source: Supporting table for Figure 6 on Page 154 of Volume 218 of Study 437 Clinical Study Report.

In Study 437, among the patients who did not have normalized ALT by Week 48, an estimated 38% (95% CI [20.7%, 55.9%]) of these patients will have ALT normalization by Week 72 if the continued treatment on adefovir 10 mg through Week 72 while only 9% (95% CI [0%, 20.3%]) of those switch to Placebo after Week 48 will have ALT normalization by Week 72. The differences between continuation of treatment in Year 2 versus discontinuation of treatment are statistically significant.

Table 15:
 Kaplan-Meier Analysis on Time to Onset of Normalization of ALT for Year 2
 (As-Treated Population with ALT > ULN at Week 48)
 —Study 438

Time Interval	Treatment Group					
	ADV 10 mg to Placebo		ADV 10 mg to ADV 10 mg		Placebo to ADV 10 mg	
	At Risk	Cumulative Events (%)	At Risk	Cumulative Events (%)	At Risk	Cumulative Events (%)
Week 48	8	0 (0%)	19	0 (0%)	42	0 (0%)
>Week 48-Week 52	8	0 (0%)	19	0 (0%)	42	7 (17%)
>Week 52-Week 56	8	0 (0%)	19	1 (5%)	35	15 (36%)
>Week 56-Week 60	8	0 (0%)	17	3 (16%)	27	16 (38%)
>Week 60-Week 64	8	0 (0%)	15	4 (22%)	25	17 (41%)
>Week 64-Week 68	8	0 (0%)	10	4 (22%)	22	22 (54%)
>Week 68-Week 72	7	0 (0%)	8	4 (22%)	16	26 (67%)
95% CI at Week 48	NA		(2.9%, 41.1%)		(51.3%, 82.5%)	
p-value (ADV 10 mg vs Placebo)†	0.1325					

† p-value is based on log-rank test.
 NOTE: 1) ALT normalization is defined as ALT ≤ ULN at the post-baseline time point for patients with ALT > ULN at baseline.
 2) Normalization of ALT is referred to as an event. Cumulative event column shows the number and percentage of patients with normalization of ALT at the end of that interval.
 3) Number of patients at risk is at the beginning of an interval. Cumulative events and KM% (95% CI) are at the end of the interval.

Source: Supporting table for Figure 6 on Page 65 of Volume 251 of Study 438 Clinical Study Report.

Similarly, in Study 438, among the patients who did not have normalized ALT by Week 48, the estimated proportion of patients who have ALT normalization in Year 2 is as follows. An estimated 22% (95% CI [2.9%, 41.1%]) of these patients will have ALT normalization by Week 72 if they continued treatment on adefovir 10 mg through Week 72. In comparison, 0% of those who switch to Placebo after Week 48 will have ALT normalization by Week 72. The differences between continuation of treatment in Year 2 versus discontinuation of treatment were not statistically significant in Study 438.

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Next we will investigate how many additional proportion of patients seroconvert in the second 48 weeks of treatment (Year 2) if they did not convert in the first 48 weeks (Year 1) in Study 437. See Table 16. Recall that Study 438 enrolled HBeAg-negative patients, so HBeAg seroconversion does not apply to this study.

Table 16:

Kaplan-Meier Analysis on Time to Onset of HBeAg Seroconversion for Year 2
 (As-Treated Population excluding Patients with Seroconversion in Year 1)
 —Study 437

Time	Treatment Group							
	ADV 30 mg to Placebo		ADV 10 mg to Placebo		ADV 10 mg to ADV 10 mg		Placebo to ADV 10 mg	
	At Risk	Cum. Events (%)	At Risk	Cum. Events (%)	At Risk	Cum. Events (%)	At Risk	Cum. Events (%)
Baseline (Week 48)	121	0 (0%)	61	0 (0%)	72	0 (0%)	131	0 (0%)
>Week 48-Week 52	121	3 (3%)	61	2 (3%)	72	3 (4%)	131	1 (1%)
>Week 52-Week 56	111	4 (4%)	56	3 (5%)	59	3 (4%)	125	8 (7%)
>Week 56-Week 60	92	5 (5%)	45	4 (8%)	52	3 (4%)	100	9 (8%)
>Week 60-Week 64	74	7 (7%)	36	5 (11%)	45	4 (7%)	86	9 (8%)
>Week 64-Week 68	61	10 (13%)	23	7 (20%)	35	4 (7%)	68	9 (8%)
>Week 68-Week 72	42	11 (15%)	18	7 (20%)	29	4 (7%)	56	11 (11%)
95% CI at Week 48	(6.3%, 23.9%)		(5.6%, 34.2%)		(0.1%, 13.7%)		(4.5%, 18.5%)	
p-value (ADV 10 mg to ADV 10 mg vs ADV 10 mg to Placebo) †	0.198							

† p-value is based on log-rank test. p-value is not statistically significant at 0.05 level of significance.

Source: Supporting table for Figure 2 on Page 108 of Volume 218 of Study 437 Clinical Study Report.

After additional 24 weeks of treatment with ADV 10 mg, i.e., at Week 72, among those who did not seroconvert in Year 1, the estimated proportion of patients that will seroconvert is 7%. However, if patients who were on ADV 10 mg in the first year and did not seroconvert, switch to Placebo (no treatment beyond 48 weeks), the estimated additional proportion of patients that will seroconvert is 20%.

Statistical Reviewer's Comments

In summary, discontinuation of adefovir treatment at Week 48 resulted in the peak of serum HBV DNA and serum ALT to levels closer to baseline. Among the patients who did not have ALT normalization after Week 48, there were significant increases in the proportion of patients with ALT normalization by Week 72 when adefovir 10 mg treatment was continued through Week 72 as compared with patients who switched to Placebo after Week 48. However, the differences in rates of ALT normalization in Year 2 were not significantly different in Study 438 when continuation of ADV 10 mg was compared with Placebo in Year 2.

Among patients who did not seroconvert (HBeAg) in Year 1, there were numerically greater proportion of patients who seroconverted at Week 72 in those who discontinued adefovir, i.e., switched to Placebo as compared with those who continued treatment with adefovir 10 mg through Week 72, although this difference was not statistically significant.

We also analyzed data on patients who experienced loss of HBeAg in Year 2, but not in Year 1. At Week 72, the additional proportion of patients who had HBeAg loss was 22% (95% CI [9.2%, 34.4%]; n=10) in patients continuing adefovir 10 mg versus 15% (95% CI [1.0%, 28.2%]; n=11) in those who discontinued (i.e., switched to Placebo after Week 48). This difference was also not statistically significant.

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2.4.3 Statistical Reviewer's Findings on Safety

2.4.3.1 Assessment of Nephrotoxicity

When adefovir was studied at substantially higher doses of 60 mg and 120 mg daily for the treatment of HIV infection, a primary treatment-emergent toxicity of adefovir was shown to be nephrotoxicity (i.e., toxicity to the kidneys). Nephrotoxicity was characterized by a delayed onset of *increase in serum creatinine* and *decrease in serum phosphorus (hypophosphatemia)* in a gradual, dose-dependent manner.

The potential risk of developing nephrotoxicity was of particular concern in patients in Study 435 who had underlying renal insufficiency and had received the adefovir 10 mg once daily dose.

Statistical Reviewer's Comments:

Note that adefovir is eliminated by the kidney. As such, significantly increased drug exposures were seen in patients who had underlying renal insufficiency. Therefore, in Study 435 which enrolled pre- and post-liver transplant patients, most of whom had some degree of underlying renal insufficiency at baseline or other risk factors for renal dysfunction during treatment, the adefovir 10 mg once daily dose may have been high enough to cause a risk of nephrotoxicity.

In comparison, patients in Studies 437 and 438 had relatively normal renal functions at baseline. Using the nonparametric survival analysis technique of Kaplan-Meier, various time-to-event analyses were performed by the Applicant for estimating the proportion of patients in Studies 437 and 438 satisfying the following criteria:

- Any increase in serum creatinine ≥ 0.3 mg/dL from baseline
- Hypophosphatemia defined as any decrease in serum phosphorus < 2.0 mg/dL
- Confirmed increase in serum creatinine ≥ 0.3 mg/dL from baseline (confirmed by laboratory values at two consecutive visits)
- Confirmed hypophosphatemia defined as confirmed decrease in serum phosphorus < 2.0 mg/dL (confirmed by laboratory values at two consecutive visits)

All available data up to 96 weeks was used to perform these analyses. As discussed in detail in the Medical Officer, Dr. Tan Nguyen's review, the overall risk of nephrotoxicity was found to be low in patients in Studies 437 and 438.

However, for Study 435, the Applicant evaluated nephrotoxicity using higher cutoff values for creatinine (≥ 0.5 mg/dL increase from baseline) and hypophosphatemia (< 1.5 mg/dL which is Grade 3 or higher toxicity). These cutoffs were considered to be more liberal.

To further evaluate the risk of nephrotoxicity we performed complimentary analyses

using the cutoff of 0.3 mg/dL for change from baseline in serum creatinine and 2.0 mg/dL as cutoff for change from baseline in serum phosphorus (hypophosphatemia).

We performed the following time-to-event analyses using the Kaplan-Meier method based on the long-term data from the Safety Update for patients in Study 435.

- Time to confirmed increase in serum creatinine ≥ 0.3 mg/dL from baseline
- Time to confirmed hypophosphatemia defined as change from baseline in phosphorus < 2.0 mg/dL

Table 17 and Table 18 below show the baseline serum creatinine and baseline serum phosphorus in Study 435.

Table 17:

Baseline Serum Creatinine in Study 435

Baseline Serum Creatinine (mg/dL)	Treatment Cohort			
	A=Post-Liver Transplant Patients B=Waitlisted for Liver Transplant Patients			
	1A n=126	2A n=12	3A n=71	Total n=209
Normal (<1.5)	82 (65%)	6 (50%)	34 (48%)	122 (58%)
Grade 1 (1.5 to 2.0)	19 (15%)	3 (25%)	13 (18%)	35 (17%)
Grade 2 (>2.0 to 3.0)	2 (2%)	0 (0%)	8 (11%)	10 (5%)
Grade 3 (>3.0 to 6.0)	1 (1%)	0 (0%)	4 (6%)	5 (2%)
Grade 4 (>6.0)	0	0	0	0
Missing values	22 (17%)	3 (25%)	12 (17%)	37 (18%)
	1B n=51	2B n=2	3B n=98	Total n=151
Normal (<1.5)	43 (84%)	2 (100%)	72 (73%)	117 (77%)
Grade 1 (1.5 to 2.0)	2 (4%)	0	5 (5%)	7 (5%)
Grade 2 (>2.0 to 3.0)	0	0	2 (2%)	2 (1%)
Grade 3 (>3.0 to 6.0)	0	0	3 (3%)	3 (2%)
Grade 4 (>6.0)	0	0	2 (2%)	2 (1%)
Missing values	6 (12%)	0	14 (14%)	20 (13%)

Source: FDA Statistical Reviewer's Analysis. NDA 21-449, NDA Safety Update electronic data

Table 18:

Baseline Serum Phosphorus in Study 435

Baseline Phosphorus (mg/dL)	Treatment Cohort			
	A=Post-Liver Transplant Patients		B=Waitlisted for Liver Transplant Patients	
	1A n=126	2A n=12	3A n=71	Total n=209
Normal (≥ 2.5)	99 (79%)	9 (75%)	54 (76%)	162 (78%)
Grade 1 (2.0 to < 2.5)	4 (3%)	0	4 (6%)	8 (4%)
Grade 2 (1.5 to < 2.0)	0	0	1 (1%)	1 ($< 1\%$)
Grade 3 (1.0 to < 1.5)	0	0	0	0
Grade 4 (< 1.0)	0	0	0	0
Missing values	23 (18%)	3 (25%)	12 (17%)	38 (18%)
	1B n=51	2B n=2	3B n=98	Total n=151
Normal (≥ 2.5)	40 (78%)	1 (50%)	74 (76%)	115 (76%)
Grade 1 (2.0 to < 2.5)	4 (8%)	0	6 (6%)	10 (7%)
Grade 2 (1.5 to < 2.0)	1 (2%)	0	3 (3%)	4 (3%)
Grade 3 (1.0 to < 1.5)	0 (0%)	1 (50%)	1 (1%)	2 (1%)
Grade 4 (< 1.0)	0	0	0	0
Missing values	6 (12%)	0 (0%)	14 (14%)	20 (13%)

Source: FDA Statistical Reviewer's Analysis. NDA 21-449, NDA Safety Update electronic data

As shown in the tables above, several patients had abnormal serum creatinine at baseline that was Grade 1 toxicity level or higher (24% of post-liver transplant patients in cohort A and 9% of waitlisted for liver-transplant patients in cohort B). Also, some patients had abnormal levels of serum phosphorus at baseline (5% of post-liver transplant patients in cohort A and 11% of waitlisted for liver-transplant patients in cohort B).

In Figure 9, Figure 10, Figure 11, and Figure 12 we show the Kaplan-Meier estimates of cumulative incidences of confirmed increase in serum creatinine from baseline ≥ 0.3 mg/dL and confirmed hypophosphatemia < 2.0 mg/dL for cohorts A and B based on all available data, along with 95% confidence intervals based on Greenwood's formula.

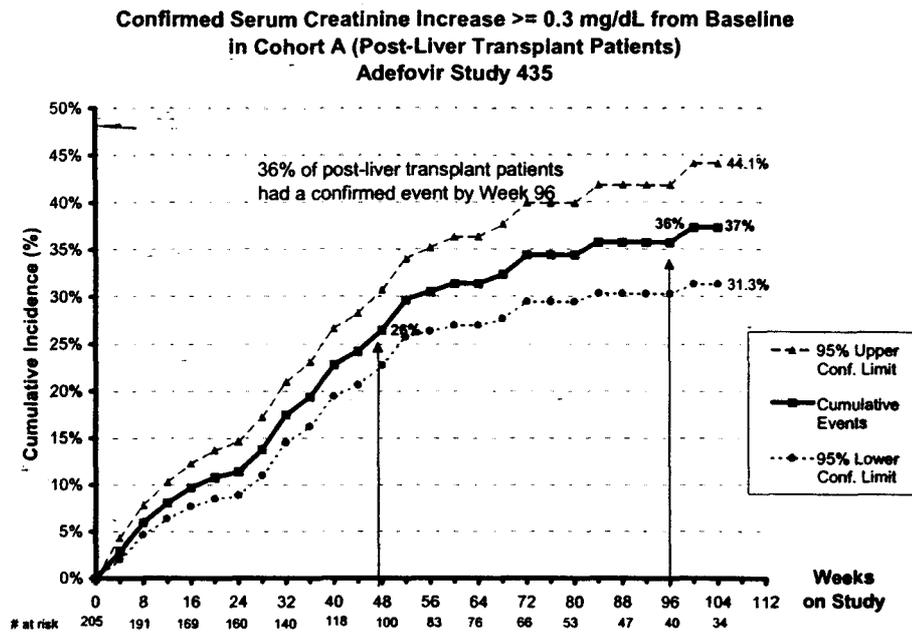


Figure 9: Confirmed Increase in Serum Creatinine ≥ 0.3 mg/dL from Baseline in Study 435 (Post-Liver Transplant Patients)

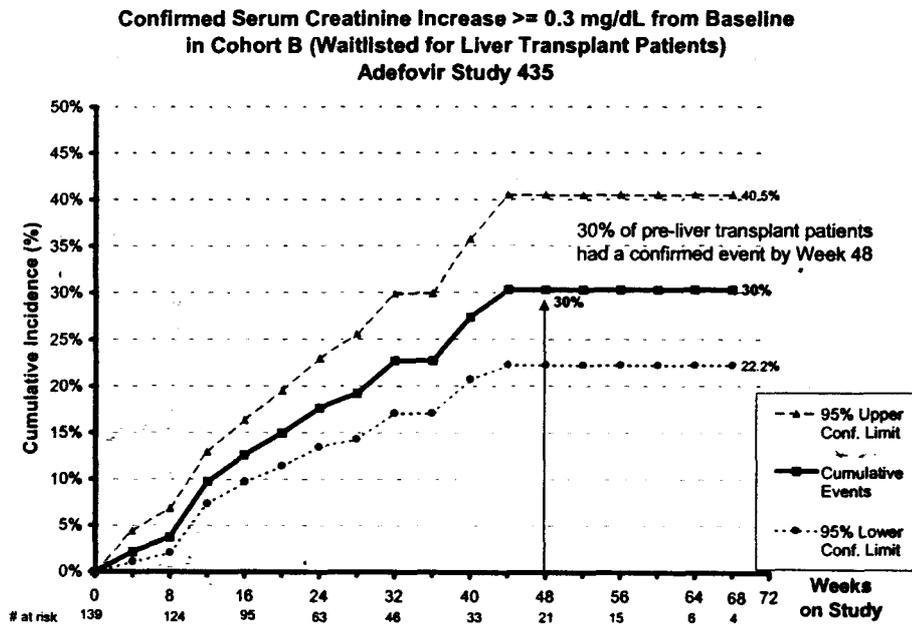


Figure 10: Confirmed Increase in Serum Creatinine ≥ 0.3 mg/dL from Baseline in Study 435 (Waitlisted for Liver Transplant Patients)

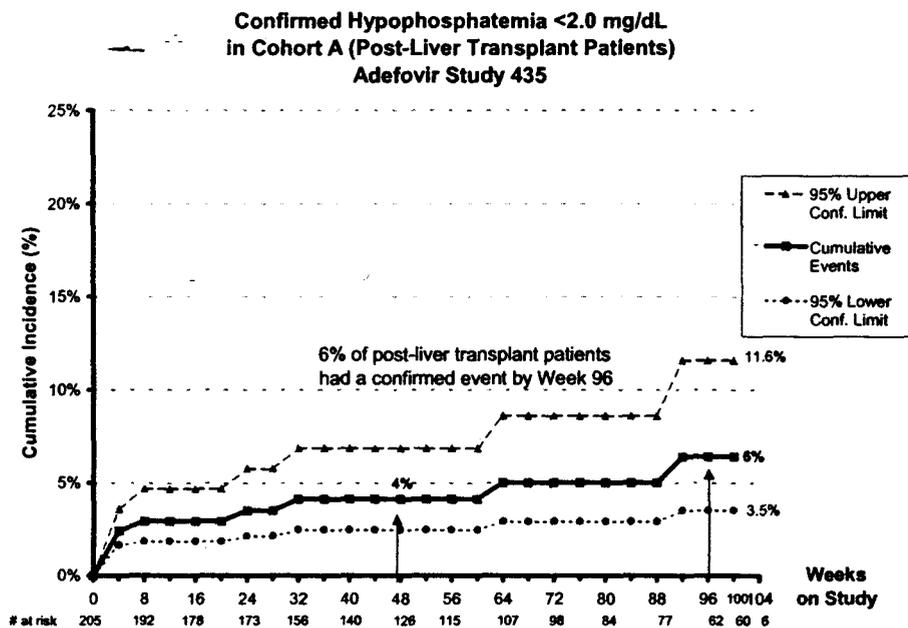


Figure 11: Confirmed Hypophosphatemia <2.0 mg/dL from Baseline in Study 435 (Post-Liver Transplant Patients)

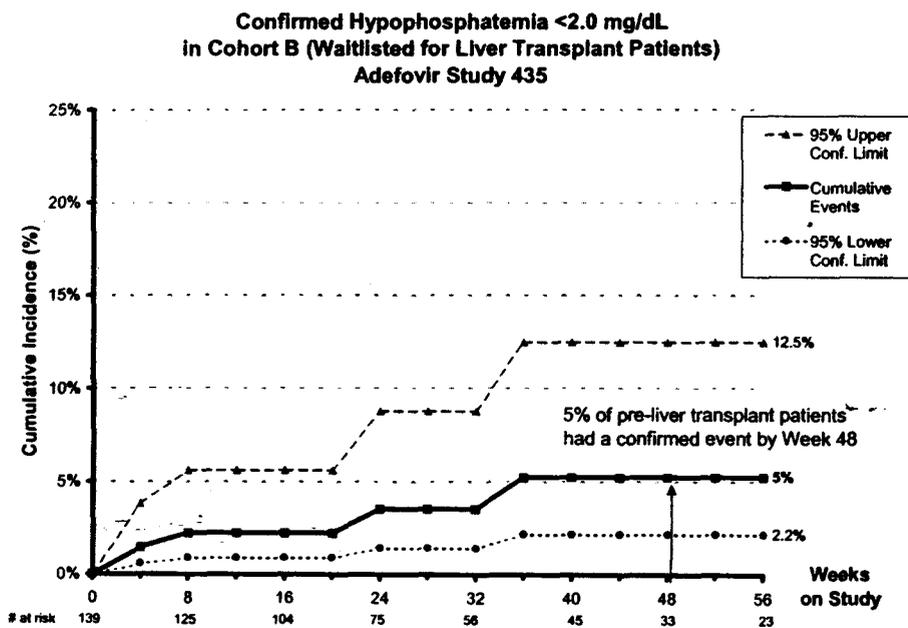


Figure 12: Confirmed Hypophosphatemia <2.0 mg/dL from Baseline in Study 435 (Waitlisted for Liver Transplant Patients)

Note that in Study 435 patients with end-stage liver disease were enrolled in whom renal function may be compromised. Also, some of these patients were taking concomitant nephrotoxic drugs. Although a number of these patients had abnormal renal functions at baseline, a substantial proportion of patients experienced treatment-emergent nephrotoxicity as characterized by increase in serum creatinine from baseline and decrease in serum phosphorus from baseline.

The findings for increase in serum creatinine were as follows.

- By Week 96, 36% of the post-liver transplant patients (cohort A) had a confirmed increase from baseline in serum creatinine ≥ 0.3 mg/dL with a 95% confidence interval of (30.3%, 41.8%).
- By Week 48, 30% of the waitlisted for liver transplant patients (cohort B) had a confirmed increase from baseline in serum creatinine ≥ 0.3 mg/dL with a 95% confidence interval of (22.2%, 40.5%).

The findings for decrease in serum phosphorus (hypophosphatemia) were as follows.

- By Week 96, 6% of the post-liver transplant patients (cohort A) had a confirmed hypophosphatemia < 2.0 mg/dL with a 95% confidence interval of (3.5%, 11.6%).
- By Week 48, 5% of the waitlisted for liver transplant patients (cohort B) had a confirmed hypophosphatemia < 2.0 mg/dL with a 95% confidence interval of (2.2%, 12.5%).

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2.5 Findings in Special/Subgroup Populations

In this section we present efficacy results for various subgroups of patients based on their gender (male vs. female), race (White, Asian, Black, or Other), and median age (<35 years vs ≥ 35 years in study 437 and <45 years vs ≥ 45 years in study 438).

Statistical Reviewer's Comments:

Since one of the main goals of therapy for chronic hepatitis B is to prevent the progression (worsening) of fibrosis of the liver and better still show regression (improvement) in fibrosis, we present subgroup analyses based on the Ishak fibrosis scores at Week 48 (post-treatment) instead of the pre-defined primary efficacy endpoint of histologic improvement (≥ 2 point reduction in necroinflammatory score with no concurrent worsening of fibrosis based on the Knodell scoring system). We reached the same conclusions regarding the subgroup populations when we analyzed the data using pre-defined primary efficacy endpoint of histologic improvement.

Additionally, the Ishak fibrosis scoring system was considered to be more precise than the Knodell scoring system for measuring fibrosis because it has more scoring points and the distance between the scores is the same through the scale of 0 to 6.

Therefore, in this section we chose to present the subgroup analyses based on the Ishak fibrosis scores.

Table 19, Table 20, and Table 21 show the proportion of patients in Studies 437 and 438 who had an improvement in fibrosis at Week 48 based on the Ishak scores. Improvement in fibrosis was defined as ≥ 1 point reduction in Ishak fibrosis score.

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Table 19:

Proportion of Patients with Improvement † in Fibrosis at Week 48
 based on Ishak Scores:
 Subgroup Analyses by Gender

	Treatment Group			Net Treatment Effect of 10mg vs Placebo (95% CI)	p-value (Treatment by Gender interaction for ADV 10mg group)
	ADV 30 mg	ADV 10 mg	Placebo		
Study 437					
Male (n=333)	51/111 (46%)	44/116 (38%)	18/106 (17%)	21% (10%, 32%)	0.047*
Female (n=115)	10/36 (28%)	8/36 (22%)	10/43 (23%)	-1.0% (-20%, 18%)	
Study 438					
Male (n=140)		33/94 (35%)	7/46 (15%)	19.9% (6%, 34%)	0.819
Female (n=29)		5/19 (26%)	1/10 (10%)	16.3% (-11%, 43%)	

Patients from ITT population with adequate biopsy pairs are used in this analysis.
 p-values are based on chi-square test.
 * p-value for treatment by subgroup interaction is statistically significant.
 † Improvement in fibrosis is defined as a 1 point or more reduction in Ishak fibrosis score.

Source: FDA Statistical Reviewer's analysis

As shown in Table 19, the magnitude of treatment effect due to ADV 10 mg relative to Placebo was larger in men as compared with women in Study 437. Approximately 20% additional men had improvement in fibrosis with ADV 10 mg relative to Placebo in both the studies. In comparison, based on Study 437, women had similar improvement in fibrosis whether they received ADV 10 mg or Placebo. Therefore, women may not have any additional therapeutic benefit due ADV 10 mg with respect to improvement in fibrosis. The difference in the magnitude of treatment effects for men vs. women was statistically significant in Study 437.

In Study 438, the number of women enrolled in each group was too small to make any statistical conclusions about differences in therapeutic benefit in men versus women. The observed treatment effect in women due to ADV 10 mg relative to Placebo was not statistically significant.

Table 20:
 Proportion of Patients with Improvement † in Fibrosis at Week 48
 based on Ishak Scores:
 Subgroup Analyses by Race

	Treatment Group			Net Treatment Effect of 10mg vs Placebo (95% CI)	p-value (Treatment by Gender interaction for ADV 10mg group)
	ADV 30 mg	ADV 10 mg	Placebo		
Study 437					
White (n=164)	24/55 (44%)	18/52 (35%)	10/57 (18%)	17.1% (1%, 33%)	0.956
Asian (n=261)	34/84 (40%)	33/91 (36%)	16/86 (19%)	17.1% (5%, 31%)	
Black (n=16)	3/5	1/8	1/3		
Other (n=7)	0/3	0/1	1/3		
Study 438					
White (n=114)		27/77 (35%)	3/37 (8%)	27.0% (13%, 41%)	0.181
Asian (n=50)		11/32 (34%)	5/18 (28%)	6.6% (-20%, 33%)	
Black (n=5)		3/4	0/1		
Other (n=0)		NA	NA		
Patients from ITT population with adequate biopsy pairs are used in this analysis. p-values are based on chi-square test. NA=not available. No patients of "other" races were enrolled. † Improvement in fibrosis is defined as a 1 point or more reduction in Ishak fibrosis score.					

Source: FDA Statistical Reviewer's analysis

As shown in Table 20, Black patients and patients of other races were underrepresented in both studies. Among the HBeAg-positive patients (Study 437), White and Asian patients had similar rates of improvement in fibrosis due to ADV 10 mg relative to Placebo. However, among the HBeAg-negative patients (Study 438), White patients had a greater rate (27%) of improvement in fibrosis as compared with the Asian patients (7%).

Table 21:

Proportion of Patients with Improvement † in Fibrosis at Week 48
 based on Ishak Scores:
 Subgroup Analyses by Age

	Treatment Group			Net Treatment Effect of 10mg vs Placebo (95% CI)	p-value (Treatment by Age interaction for ADV 10mg group)
	ADV 30 mg	ADV 10 mg	Placebo		
Study 437					
<35 years (n=237)	33/88 (37%)	27/85 (32%)	12/64 (19%)	13.0% (-1%, 27%)	0.588
>=35 years (n=211)	28/59 (47%)	25/67 (37%)	16/85 (19%)	18.5% (4%, 33%)	
Study 438					
<45 years (n=71)		14/46 (30%)	5/25 (20%)	10.4% (-10%, 31%)	0.232
>=45 years (n=98)		24/67 (36%)	3/31 (10%)	26.1% (11%, 42%)	
Patients from ITT population with adequate biopsy pairs are used in this analysis. p-values are based on chi-square test. NOTE: The age distribution in the two studies were different. The median age in Study 437 was 33 years and in Study 438 the median age was 46 years. Hence the age splits used in the two studies are different for this subgroup analysis. † Improvement in fibrosis is defined as a 1 point or more reduction in Ishak fibrosis score.					

Source: FDA Statistical Reviewer's analysis

Additional subgroup analyses were also conducted based on the median age of patients in each study. Since Study 437 had younger patients than those in Study 438, the median ages in the two studies were considered separately. In both studies, the additional therapeutic benefit due to ADV 10 mg relative to Placebo was similar among whether the patients were younger or older.

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3. CONCLUSIONS AND RECOMMENDATIONS

Studies 437 and 438 which were double-blind, placebo-controlled, multicenter studies were conducted multinationally in the United States, Canada, Australia, France, Germany, Italy, Spain, United Kingdom, Taiwan, Thailand, Malaysia, Singapore, and the Phillipines. Study 437 enrolled 515 patients who were tested positive for the Hepatitis B e Antigen at baseline (HBeAg+) and in Study 438, 185 patients tested HBeAg-negative were enrolled. Study 435 was an open-label single arm study to evaluate safety and effectiveness of adefovir 10 mg once daily conducted in chronic hepatitis B patients who either received a liver-transplant (n=196) or were waitlisted for liver transplant (n=128). Study 461 is an ongoing active-control study (n=59 enrolled) to evaluate effectiveness of monotherapy vs. dual therapy. Both, Studies 435 and 461 enrolled patients with lamivudine-resistant HBV.

In all studies, patients were predominantly male (approximately 75% or more). Also, patients in all studies were primarily of White or Asian ethnic origin. In Study 437 (HBeAg+) approximately 2/3rds of the patients were Asian while in Studies 438 (HBeAg-) and 435, approximately 2/3rds of the patients were White. Note that these studies were multinational studies with patients of different races enrolled in different countries.

The median baseline serum HBV DNA level in Study 437 was higher (8.36 log₁₀ copies/mL) than that in Study 438 (7.08 log₁₀ copies/mL). However, the median ALT at baseline in both studies were similar and so were the mean Knodell necroinflammatory and fibrosis scores.

Based on all the available data through Week 48 and beyond, in Studies 437, 438, and 435 as well as data through 16 weeks in Study 461 we reached the following conclusions.

1. Based on the epidemiology of chronic hepatitis B, the prevalence of hepatitis B virus infection in the United States is higher among African-Americans and Hispanics than in patients of White origin. As such, these patient populations were significantly under-represented in the Applicant's drug development program.
2. In Study 437, a statistically significantly greater proportion of patients receiving adefovir (ADV) 30 mg or 10 mg once daily showed histologic improvement (as defined by the primary efficacy endpoint of 2 point or more reduction in Knodell necroinflammatory score with no concurrent worsening of fibrosis) as compared with Placebo at Week 48. A similar result was observed for the ADV 10 mg daily dose in Study 438.

At Week 48, the observed treatment difference in Study 437 for ADV 30 mg vs. Placebo was 34.5% with a 95% confidence interval of (24%, 44%), while the observed treatment difference for ADV 10 mg versus Placebo was 27.5% with a 95% confidence interval of (17%, 37%). In Study 438, the observed treatment effect was 29.4% for ADV 10 mg vs. Placebo with a 95% confidence interval of (14%, 44%).

3. Additional analyses based on the Ishak scoring system were done to evaluate the treatment effect on fibrosis at Week 48 because of two reasons: a) changes in fibrosis were considered

to be clinically relevant in evaluating the treatment of chronic hepatitis B (which is a liver disease) and b) the Ishak scoring system is a more detailed and precise scoring system than the Knodell scoring system used in the primary efficacy endpoint.

In both studies, 437 and 438, based on the Ishak scores, a statistically significantly greater proportion of patients treated in the adefovir groups (30 mg or 10 mg) showed improvement in fibrosis relative to Placebo at Week 48.

4. With respect to the virologic response based on change from baseline in serum HBV DNA (Roche Amplicor PCR assay), the mean reduction in serum HBV DNA in the ADV 10 mg group (-3.52 log₁₀ copies/mL in Study 437 and -3.54 log₁₀ copies/mL in Study 438) was significantly greater than the mean reduction in the Placebo group (-0.99 log₁₀ copies/mL in Study 437 and -1.23 log₁₀ copies/mL in Study 438).

Also, the mean reduction in serum HBV DNA in the ADV 30 mg (-4.38 log₁₀ copies/mL in Study 437) was significantly greater than that in the ADV 10 mg group.

5. Upon continued treatment with ADV 10 mg up to 72 weeks, the viral suppression that was observed at Week 48 was maintained in both studies. However, when treatment was discontinued at Week 48, the HBV DNA levels in patients returned to levels closer to baseline.
6. Among the patients with lamivudine-resistant HBV in Studies 435 and 461, significant reduction in the serum HBV DNA was also seen upon treatment with ADV 10 mg. In Study 435, a mean reduction in serum HBV DNA of approximately 4 log₁₀ copies/mL was observed at Week 48 while in Study 461 a mean reduction of approximately 2.9 log₁₀ copies/mL was observed at Week 16 when treated with ADV 10 mg once daily. Study 461 is an ongoing study, in which the monotherapy arm (ADV 10 mg) and the dual therapy arm (ADV 10 mg + LAM 100 mg) provided similar viral suppression and both had statistically significantly greater reduction in HBV DNA relative the monotherapy with LAM 100 mg at Week 16.
7. With respect to the biochemical response: The proportion of patients with normalization of ALT in Studies 437 and 438 were significantly greater in the adefovir groups (30 mg or 10 mg) than the Placebo group. Mean reductions in ALT levels were significantly lower in the ADV 10 mg group relative to Placebo through 48 Weeks. However, when adefovir treatment was discontinued after Week 48, ALT levels peaked within 12 weeks and returned to baseline levels. This phenomenon may result in exacerbation of hepatitis B in patients.

Among the patients who did not have ALT normalization by Week 48, the additional rates of ALT normalization were evaluated in Year 2 for Studies 437 and 438. In Study 437, among these patients, the proportion of patients with ALT normalization in Year 2 was significantly higher when patients continued treatment with adefovir 10 mg up to 72 weeks (38%; 95% CI [20.7%, 55.9%]) relative to Placebo (9%; 95% CI [0%, 20.3%]).

However, these differences were not statistically significant for Study 438 (22%; 95% CI [2.9%, 41.1%]) patients with ALT normalization in ADV 10 mg group continued up to 72

weeks and 0% in the patients who switched to Placebo group up to 72 weeks.). The number of patients followed through Week 72 was only 8 patients in the ADV 10 mg group and 7 patients in the Placebo group, which is too small to detect any significant differences.

8. With respect to the serologic response: The proportion of patients who had HBeAg seroconversion in Study 437 based on Kaplan-Meier analysis was estimated to be 17% in ADV 30 mg group, 14% in the ADV 10 mg group and 9% in the Placebo group at Week 48. These differences in the estimated rates for ADV groups relative to Placebo were only marginally statistically significant.

Among patients who did not seroconvert (HBeAg) in Year 1, there were numerically greater proportion of patients who seroconverted at Week 72 in those who discontinued adefovir, i.e., switched to Placebo (20%; 95% CI [5.6%, 34.2%]) as compared with those who continued treatment with adefovir 10 mg (7%; 95% CI [0.1%, 13.7%]) through Week 72. This difference was not statistically significant.

We also analyzed data on patients who experienced loss of HBeAg in Year 2, but not in Year 1. At Week 72, the additional proportion of patients who had HBeAg loss was 22% (95% CI [9.2%, 34.4%]; n=10) in patients continuing adefovir 10 mg versus 15% (95% CI [1.0%, 28.2%]; n=11) in those who discontinued (i.e., switched to Placebo after Week 48). This difference was also not statistically significant.

9. Histologic response as measured by proportion of patients with improvement in fibrosis based on Ishak scores was evaluated in various subgroups of patients by gender, race and age. The same conclusions were reached when subgroup analyses were done using the primary endpoint of histologic improvement.

Based on Study 437, approximately 20% additional men are estimated to have improvement in fibrosis when treated with ADV 10 mg as compared with Placebo. However, in Study 437, similar proportion of women had improvement in fibrosis whether they received ADV 10 mg or Placebo. Therefore, among HBeAg+ patients, men had greater therapeutic benefit in terms of improvement in fibrosis with adefovir 10 mg treatment (relative to Placebo) than women. In Study 438, the subgroup of women patients was small in order to make any statistical conclusions about the differences in therapeutic benefit in men versus women.

Among HBeAg+ patients, White and Asian patients showed similar rates of improvement in fibrosis in Study 438. In Study 438, among HBeAg- patients, White patients had a greater rate of improvement in fibrosis with ADV 10 mg (relative to Placebo) as compared with Asian patients.

In both studies, the additional therapeutic benefit due to ADV 10 mg in terms of improvement in fibrosis was similar among younger or older patients (based on median age of enrolled patients).

10. A quantitative assessment of nephrotoxicity due to adefovir as characterized by increase in serum creatinine and hypophosphatemia was also made. This was done by performing time-to-event analyses using the Kaplan-Meier method for estimating the cumulative incidence of patients who met the criteria of increase in serum creatinine ≥ 0.3 mg/dL from baseline and decrease in serum phosphorus < 2.0 mg/dL.

When adefovir 10 mg once daily was given to patients with normal renal functions (Studies 437 and 438), the overall risk of nephrotoxicity was found to be low. However, patients with end-stage liver disease in Study 435 were found to be at high risk of nephrotoxicity when administered adefovir 10 mg once daily. Since these patients had compromised renal function, took concomitant nephrotoxic drugs and adefovir is excreted renally, these patients had significantly higher exposures of the drug when given the 10 mg daily dose. Nevertheless, a substantial proportion of these patients were found to have experienced treatment-emergent nephrotoxicity as mentioned below.

- By Week 96, 36% of the post-liver transplant patients (cohort A) had a confirmed increase from baseline in serum creatinine ≥ 0.3 mg/dL with a 95% confidence interval of (30.3%, 41.8%).
 - By Week 48, 30% of the waitlisted for liver transplant patients (cohort B) had a confirmed increase from baseline in serum creatinine ≥ 0.3 mg/dL with a 95% confidence interval of (22.2%, 40.5%).
 - By Week 96, 6% of the post-liver transplant patients (cohort A) had a confirmed hypophosphatemia < 2.0 mg/dL with a 95% confidence interval of (3.5%, 11.6%).
 - By Week 48, 5% of the waitlisted for liver transplant patients (cohort B) had a confirmed hypophosphatemia < 2.0 mg/dL with a 95% confidence interval of (2.2%, 12.5%).
11. In summary, the ADV 10 mg once daily dose for which the Applicant seeks approval showed statistically significant benefit relative to Placebo as measured by the histologic responses, virologic response (serum HBV DNA) and biochemical response (ALT) through 48 weeks of treatment. Serologic response as measured by HBeAg seroconversion at Week 48 was only marginally significant in the ADV 10 mg treated group relative to Placebo. This may be due to the naturally fluctuating nature of the disease in which patients may have spontaneous seroconversions.

The duration of therapy in treating chronic hepatitis B patients has not yet been established. Upon discontinuation of treatment with adefovir 10 mg once daily, patients had elevations in both serum HBV DNA levels and ALT levels which may not be beneficial to patients. Continued treatment beyond 48 weeks was beneficial with respect to maintaining the viral suppression and normalization of ALT levels. The effect of continued treatment with adefovir beyond 48 weeks on the loss of HBeAg and HBeAg seroconversion was statistically inconclusive.

The overall risk of nephrotoxicity was low in patients with normal renal functions. However, patients with underlying abnormal renal function were found to be at high risk for developing nephrotoxicity.

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