

Study No.: ADF105220
Title: Phase III study of adefovir dipivoxil (ADV) tablets in patients with compensated chronic hepatitis B -comparative study against lamivudine (LAM)-
Rationale: This study was a confirmatory study to evaluate the efficacy and safety of adefovir (ADV) 10mg monotherapy in Japanese subjects with compensated chronic hepatitis B in which abnormality of hepatic function accompanied by continuous replication of hepatitis B has been confirmed.
Phase: III
Study Period: 12 Jan. 2006 - 16 Jan. 2008
Study Design: Multicentre, active-controlled, double-blind, randomized, parallel-group comparative study
Centres: 15 centres in Japan
Indication: Compensated chronic hepatitis B
Treatment: ADV 10mg or lamivudine (LAM) 100mg was administered orally once daily for 52 weeks to Japanese subjects with compensated chronic hepatitis B who were naïve to antiviral medications. The study period consisted of a screening period (6 weeks or less before initiation of treatment), treatment period (52 weeks) and 24 week follow-up period for subjects who did not continue anti-HBV treatment after completion of administration of the investigational product.
Objectives: Primary objective: To compare the efficacy and safety of ADV 10mg with LAM 100mg, once daily for 52 weeks in Japanese subjects with compensated chronic hepatitis B who have not been treated with antiviral medication. For efficacy, to test the non-inferiority of ADV against LAM. Secondary objective: To compare the efficacy of ADV in monotherapy in this study to these in overseas studies (Studies GS-98-437 and GS-98-438).
Primary Outcome/Efficacy Variable: Change from baseline in serum HBV DNA level at Week 52
Secondary Outcome/Efficacy Variable(s): 1) Evaluation of HBV DNA level •Percentage of subjects with serum HBV DNA levels below the limit of quantification (HBV DNA loss) Time to onset of serum HBV DNA loss 2) Evaluation of virus markers other than HBV DNA •Percentage of subjects with HBeAg loss •Percentage of subjects with HBeAg/Ab seroconversion Time to onset of HBeAg loss Time to onset of HBeAg/Ab seroconversion •Percentage of subjects with HBsAg loss •Percentage of subjects with HBsAg/Ab seroconversion 3) Liver function tests •Alanine aminotransferase (ALT) level at Week 52 (distribution) •Percentage of subjects with normalized ALT Time to onset of ALT normalization 4) Rate of emergence of resistant virus at Week 52
Statistical Methods: The primary efficacy population was the Per Protocol Set (PPS). In addition, the Full Analysis Set (FAS) population was used to assess the robustness of the analysis. FAS was defined as all subjects who entered the study, received at least one dose of investigational product, and had at least one efficacy assessment after the treatment initiation. PPS was defined as the subjects in the FAS population with no major protocol violations. The Safety Population (SP) was defined as the subjects who received at least one dose of investigational product. The Follow-up Population (FP) was defined as all subjects who discontinued antiviral medications after the

treatment period and entered the follow-up period.

For the primary efficacy endpoint, change from baseline in serum HBV DNA level at Week 52, summary statistics and the corresponding two-sided 95% confidence intervals were calculated by treatment group. Mean and standard deviation were illustrated. Non-inferiority of ADV against LAM was tested with the statistical hypothesis using analysis of covariance model. One-sided p-value for the treatment effect was computed, and statistical significance of non-inferiority test was determined from the p-value with a significance level of 0.025. The comparisons for the secondary efficacy measures were performed based on 95% two-sided confidence interval or tested with a 0.05 two-sided significance level. For time to event variables, the Kaplan-Meier estimates were calculated by treatment group and the Log-rank test was performed to compare the difference between the treatment groups. For the percentage of subjects with resistant strains at Week 52, the comparison between ADV and LAM was performed using Fisher's exact test.

Study Population: Male or female subjects aged ≥ 16 and < 65 with compensated chronic hepatitis B who had not been treated with antiviral medications with activity against HBV (e.g. LAM, ADV, entecavir, excluding interferon [IFN]), with serum HBV DNA $\geq 1 \times 10^6$ copies/mL; serum ALT level 50-500U/L; and with no mutation resistant to ADV or LAM at screening.

	ADV	LAM
Number of Subjects:		
Planned, N	50	50
Randomised, N	52	53
Completed, n (%)	50 (96.2)	47 (88.7)
Moved into the follow-up period, n	9	5
Total Number Subjects Withdrawn, N (%)	2 (3.8)	6 (11.3)
Moved into the follow-up period, n	1	0
Withdrawn due to Adverse Events n (%)	0	6(11.3)
Withdrawn due to Lack of Efficacy n (%)	0	0
Withdrawn for other reasons n (%)	2(3.8)	0
Demographics	ADV	LAM
N (PPS)	50	52
Females: Males	9:41	17:35
Mean Age, years (SD)	44.0 (9.73)	43.9 (9.95)
Race, n (%)		
Asian	50 (100)	52 (100)
Primary Efficacy Results: (PPS)		
	ADV (N=50)	LAM (N=52)
Change from Baseline in HBV DNA at Week 52 (\log_{10} copies/mL)		
n	50	52
Mean (SD)	-3.69 (1.169)	-3.40 (1.896)
Median (range)	-3.50 (-6.1 to -0.6)	-4.00 (-6.7 to 1.5)
Least Squares Means (SE) ¹	-3.71 (0.220)	-3.38 (0.216)
Differences of Least Squares Means (ADV - LAM) (\log_{10} copies/mL)¹		
Estimate (SE)	-0.33 (0.309)	
95% CI	-0.94 to 0.28	
Non-inferiority Test based on Model: $y(\Delta) = \text{Baseline} + \text{Group}^2$		
p-value	p<0.001	
LOCF was applied to missing value. 1. Based on Model: $y = \text{Baseline} + \text{Group}$ (y: Change from Baseline in HBV DNA at Week 52) 2. $y(\Delta)$ is Change from Baseline in HBV DNA at Week 52 for LAM, and Change from Baseline in HBV DNA at Week 52 + Δ for ADV, Δ : Non-inferiority Margin (-1.0)		

Secondary Outcome Variable(s):(PPS)			
		ADV	LAM
Percentage of subjects with HBV DNA loss (< 400 copies/mL)			
	N	50	52
Baseline	n ¹ (%)	0	0
Week 52	n ¹ (%)	23 (46.0)	26 (50.0)
1. Subjects with HBV DNA < 400 copies/mL, Missing HBV DNA data treated as ≥ 400 copies/mL			
Time to onset of serum HBV DNA loss (< 400 copies/mL)			
N		50	52
n (Subjects with HBV DNA<400 Copies/mL)		24	31
Censored		26	21
Median(Week)		-	28.0
95%CI Lower		36.0	20.0
95%CI Upper		-	-
Log-Rank Test	Chi-Square	1.795	
Percentage of subjects with HBeAg Loss			
	N ¹	36	37
Week 52	n ² (%)	6 (16.7)	6 (16.2)
1. Positive HBeAg at Baseline 2. Subjects with HBeAg Loss			
Percentage of subjects with HBeAg/Ab Seroconversion			
	N ¹	31	34
Week 52	n ² (%)	3 (9.7)	2 (5.9)
1. Positive HBeAg and Negative HBeAb at Baseline 2. Subjects with HBeAg/Ab Seroconversion			
Time to onset of HBeAg loss			
N (Positive HBeAg at Baseline)		36	37
n (Subjects with HBeAg Loss)		6	6
Censored		30	31
Median(Week)		-	-
95%CI Lower		-	-
95%CI Upper		-	-
Log-Rank Test	Chi-Square	0.002	
Time to onset of HBeAg/Ab seroconversion			
N (Positive HBeAg and Negative HBeAb at Baseline)		31	34
n (Subjects with HBeAg/Ab Seroconversion)		3	3
Censored		28	31
Median(Week)		-	-
95%CI Lower		-	-
95%CI Upper		-	-
Log-Rank Test	Chi-Square	0.008	
Percentage of subjects with HBsAg Loss			
	N ¹	50	52
Week 52	n ² (%)	0	0
1. Positive HBsAg at Baseline 2. Subjects with HBsAg Loss			
Percentage of subjects with HBsAg/Ab Seroconversion			
	N ¹	46	45

Week 52	n ² (%)	0	0
1. Positive HBsAg and Negative HBsAb at Baseline 2. Subjects with HBsAg/Ab Seroconversion			
ALT (U/L)			
Baseline	n	50	52
	Mean (SD)	126.3 (121.41)	158.1 (126.33)
	Median (range)	83.5 (36 to 600)	128.0 (44 to 568)
Week 52	n	50	47
	Mean (SD)	32.3 (14.72)	33.0 (28.12)
	Median (range)	28.5 (14 to 85)	25.0 (9 to 153)
Percentage of subjects with ALT Normalization			
	N ¹	46	51
Week 52	n ² (%)	38 (82.6)	40 (78.4)
1. Subjects with ALT > the upper limit of the normal range (ULN) at Baseline 2. %: Numbers of subjects with ALT Normalization / numbers of subjects with ALT > ULN at baseline			
Time to onset of ALT normalization			
		ADV	LAM
N (Subjects with ALT > ULN at Baseline)		46	51
n (Subjects with ALT Normalization)		40	46
Censored		6	5
Median(Week)		12.0	12.0
95%CI Lower		8.0	12.0
95%CI Upper		16.0	16.0
Log-Rank Test	Chi-Square	0.001	
Rate of Emergence of Resistant Virus at Week 52			
	N	50	52
Week 52	n ¹ (%)	0	15 (28.8)
1. Subjects with resistant (LOCF was applied to missing data)			

Comparison of Changes from Baseline in HBV DNA level between the Japanese (FAS) and overseas studies (ITT: Studies GS-98-437 and GS-98-438)				
		ADF105220 (This study) ADV 10mg (FAS) N=51	GS-98-437 ADV 10mg (ITT) N=171	GS-98-438 ADV 10mg (ITT) N=123
HBV DNA at baseline (log ₁₀ copies/mL)	n	51	171	123
	Median	7.20	8.40	7.10
	Q1 to Q3	6.40 to 8.80	7.69 to 8.87	6.35 to 7.53
	Range	5.3 to 9.9	5.24 to 10.16	3.67 to 9.46
Change from baseline in HBV DNA at Week48 (log ₁₀ copies/mL)	n	50	152	117
	Median	-3.65	-3.52	-3.91
	Q1 to Q3	-4.60 to -2.80	-4.91 to -2.22	-4.51 to -2.98
	Range	-6.1 to -1.1	-6.78 to 0.68	-5.82 to -0.09

Safety Results:

	ADV (N=52)	LAM (N=53)
Most Frequent Adverse Events – On-Therapy		
Subjects with any AE(s), n(%)	39 (75)	47 (89)
Most Frequent AEs (the most frequent 10 events in each group) up to Week 52 - On-Therapy		
Nasopharyngitis	11 (21)	19 (36)
Diarrhoea	7 (13)	6 (11)
Upper respiratory tract inflammation	7 (13)	10 (19)
Eczema	5 (10)	3 (6)
Blood creatine phosphokinase increased	5 (10)	4 (8)
Abdominal pain upper	3 (6)	2 (4)
Arthralgia	3 (6)	0
Gastritis	2 (4)	2 (4)
Abdominal pain lower	2 (4)	1 (2)
Stomatitis	2 (4)	0
Pharyngolaryngeal pain	2 (4)	5 (10)
Cough	2 (4)	3 (6)
Rhinorrhoea	2 (4)	0
Asteatosis	2 (4)	0
Malaise	2 (4)	5 (10)
Chest pain	2 (4)	0
Myalgia	2 (4)	1 (2)
Dizziness	2 (4)	0
Nausea	1 (2)	4 (7)
Headache	1 (2)	4 (7)
Hepatitis	0	6 (11)
Vomiting	0	3 (6)
Drug-related Adverse Events-On-Therapy		
	ADV (N=52)	LAM (N=53)
Subjects with any drug-related AEs, n(%)	4 (8)	11 (21)
Drug-related AEs up to Week 52 - On-Therapy		
Palpitations	1 (2)	1 (2)
Anaemia	1 (2)	0
Iron deficiency anaemia	1 (2)	0
Gastritis	1 (2)	1 (2)
Rash	1 (2)	0
Hepatitis	0	6 (11)
Headache	0	3 (6)
Gastric polyps	0	1 (2)
Nausea	0	1 (2)
Stomach discomfort	0	1 (2)
Dermatitis acneiform	0	1 (2)
Toxic skin eruption	0	1 (2)
Somnolence	0	1 (2)
Malaise	0	1 (2)
Serious Adverse Events - On-Therapy		
n(%) [n considered by the investigator to be related to study medication]		
	ADV (N=52)	LAM (N=53)
	n (%) [related]	n (%) [related]
Subjects with non-fatal SAEs, n (%)	0	4 (7), [1]

Hepatitis	0	1 (2), [1]
Pneumonia bacterial	0	1 (2), [0]
Lymphoma	0	1 (2), [0]
Urinary retention	0	1 (2), [0]
	n (%) [related]	n (%) [related]
Subjects with fatal SAEs, n (%)	0	0
Adverse Events - Follow-up period		
	ADV (N=10)	LAM (N=5)
Subjects with any AEs, n(%)	7 (70)	5 (100)
AEs in the follow-up period		
Nasopharyngitis	2 (20)	2 (40)
Fatigue	2 (20)	0
Blood creatine phosphokinase increased	2 (20)	1 (20)
Cellulitis	1 (10)	0
Tonsillitis	1 (10)	0
Abdominal pain upper	1 (10)	0
Colonic polyp	1 (10)	0
Diarrhoea	1 (10)	0
Fasciitis	1 (10)	0
Fractured coccyx	1 (10)	0
Dizziness	1 (10)	0
Rash	1 (10)	0
Pharyngitis	0	2 (40)
Malaise	0	1 (20)
Drug-related Adverse Events - Follow-up period		
Subjects with any drug-related AEs, n(%)	0	0
Serious Adverse Event - Follow-up period		
Subjects with non-fatal SAEs, n (%)	0	0
Subjects with fatal SAEs, n (%)	0	0

Conclusion:

The efficacy profile of ADV 10mg once a day was investigated in this study with a primary efficacy endpoint of change from baseline of HBV DNA level at Week 52. The efficacy of ADV was confirmed as non-inferior compared to that of LAM (by analysis of covariance, one-sided p-value, $p < 0.001$).

Compared to the overseas studies, the median change from baseline in HBV DNA level at Week 48 in this study (FAS: $-3.65 \log_{10}$ copies/mL) was similar to those in GS-98-437 (ITT: $-3.52 \log_{10}$ copies/mL) and GS-98-438 (ITT: $-3.91 \log_{10}$ copies/mL). This result supported the validity of the dosage and administration in Japanese subjects with 10mg once a day.

The percentage of subjects with HBV DNA loss in both treatment groups at Week 52 was similar with 46.0% and 50.0%, respectively, and there was no statistically significant difference in time to onset of serum HBV DNA loss between the ADV group and the LAM group (Log-rank Test).

The numbers of subjects with HBeAg loss (percentage of subjects with positive HBeAg at baseline) in the ADV group and the LAM group at Week 52 were 6/36 (16.7%) and 6/37 (16.2%), respectively. The seroconversion rate of HBeAg/Ab (percentage of subjects with positive HBeAg and negative HBeAb at baseline) in the ADV group and the LAM group at Week 52 was 9.7% (3/31) and 5.9% (2/34), respectively.

There was no difference in time to onset of HBeAg loss and HBeAg/Ab seroconversion between the ADV group and the LAM group (Log-rank Test).

Although ALT values varied at baseline, they were somewhat higher in the LAM group. A significant improvement was noted in both groups at Week 52, and was equivalent to that seen

in the LAM group. The median (range) ALT levels in the ADV group and the LAM group at Week 52 were 28.5 (14 to 85) and 25.0 (9 to 153) U/L, respectively. The numbers of subjects with ALT normalization (percentage of subjects with ALT levels over ULN at baseline) in the ADV group and the LAM group at Week 52 were 38/46 (82.6%) and 40/51 (78.4%), respectively. There was no difference in time to onset of ALT normalization between the ADV group and the LAM group (Log-rank Test).

No emergence of resistance mutations up to Week 52 (treatment completion) in the ADV group (0/50 subjects), whereas the emergence of resistance mutations was markedly noted in the LAM group [15/52 subjects (28.8%)].

In the ADV group 39 subjects reported adverse events with the most frequently reported being nasopharyngitis, diarrhoea and upper respiratory tract inflammation. In LAM group 47 subjects reported adverse events with the most frequently reported being nasopharyngitis, upper respiratory tract inflammation, diarrhoea and hepatitis. The incidence of the drug-related AEs in the ADV group was lower compared with the LAM group. Four subjects (4/52, 7.7%) reported drug-related AEs in the ADV group and 11 subjects (11/53, 20.8%) reported drug-related AEs in the LAM group. No deaths were reported in either treatment group. There was no SAE in the ADV group. Four non-fatal SAEs were reported in the LAM group, they included hepatitis, pneumonia bacterial, lymphoma and urinary retention. Of four SAEs, one event of hepatitis was considered to be related to study drug by the investigator.

Since 15 subjects (10 in the ADV group and 5 in the LAM group) discontinued the anti-viral therapy, they moved into 24-week follow-up period. As a result, neither clinically significant aggravation after study treatment nor serious outcome was reported. No death, SAE, or drug-related AE were reported during the follow-up period.

Publications: No Publication