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<b>Study No.:</b> ADF30003		
<b>Title:</b> Clinical evaluation of adefovir dipivoxil (GW284873X) in patients with chronic hepatitis B (including cirrhosis B) who have signs of clinical deterioration associated with the replication of YMDD variant HBV following lamivudine therapy – A follow-up long-term study of ADF30002 (a 16-week, open label study).		
<b>Rationale:</b> This study was planned to provide treatment with adefovir dipivoxil to subjects who were enrolled in study ADF30002 (in chronic hepatitis B subjects [including those with cirrhosis] who developed YMDD mutant hepatitis B virus [HBV] and abnormal liver function while receiving lamivudine) and to subjects who were enrolled in study 714LC-02 (study on lamivudine in subjects with cirrhosis) and developed YMDD mutant HBV while receiving lamivudine in the study. The safety and efficacy of long-term oral concomitant administration of adefovir dipivoxil 10mg tablet and lamivudine 100mg tablet (1 tablet each), given once daily for 48 weeks or more, were investigated in those subjects. This study was conducted until approval of adefovir dipivoxil in Japan.		
<b>Phase:</b> III		
<b>Study Period:</b> June 2003 – December 2004		
<b>Study Design:</b> Open-label, multi-centre study		
<b>Centres:</b> 16 active centres in Japan.		
<b>Indication:</b> Combination with lamivudine for improvement of virological markers and liver function in adult subjects with the following diseases who have evidence of abnormal liver function associated with persistent hepatitis B virus (HBV) replication while receiving lamivudine monotherapy: Chronic hepatitis B and hepatitis B-related cirrhosis.		
<b>Treatment:</b> Subjects received adefovir dipivoxil (10mg tablet, oral administration) and lamivudine (100mg tablet, oral administration) once daily.		
<b>Objectives:</b> To evaluate the safety and efficacy of long-term concomitant administration of adefovir dipivoxil 10mg tablet and lamivudine 100mg tablet, in chronic hepatitis B subjects (including those with cirrhosis) who had been enrolled in study ADF30002 or study 714LC-02.		
<b>Primary Outcome/Efficacy Variable:</b> 1) Time-weighted change in log <sub>10</sub> HBV DNA from baseline up to 84 weeks (DAVG <sub>84</sub> ). 2) Change in ALT level at 84 weeks from baseline.		
<b>Secondary Outcome/Efficacy Variable(s):</b> a) Serologic Measures: Proportion of subjects with HBeAg loss; Proportion of subjects with HBeAg/Ab seroconversion b) Virologic Measures: Proportion of subjects with serum HBV DNA levels below the limit of quantification (HBV DNA < 400 copies/mL) at each study visit c) Liver Function Tests: Proportion of subjects achieving normal serum ALT at week 48; Time to onset of confirmed serum ALT normalization		
<b>Statistical Methods:</b> FAS was defined as a group of subjects excluding those who had not received one dose of study medication, and/or those who had not been evaluated for efficacy. SP was defined as a group of subjects who had received at least one dose of study medication. FAS was used for the efficacy analysis, and SP was used for the safety analysis; subjects, however, who had been progressed from Cohort 1 to Cohort 2, and subjects who had been transferred from study 714LC-02 were excluded from these analyses (Efficacy and safety results of these subjects were not analysed but only presented in listings.). For the primary analysis, the variation in serum HBV DNA (DAVG <sub>84</sub> ), time-weighted changes in log <sub>10</sub> HBV DNA (DAVG <sub>84</sub> ) from baseline (on screening and immediately before the start of treatment in study ADF30002) to week 84 of treatment were calculated and the 95% confidence interval (CI) estimated. For the effect on ALT, changes from immediately before the start of treatment in study ADF30002 to week 84 were calculated and the 95% CI estimated.		
<b>Study Population:</b> The key inclusion criteria of study ADF30002 were HBV-DNA level $\geq 10^6$ copies/mL, ALT level; 50-500 IU/L, albumin level; $\geq 3.0$ g/dL, total bilirubin level; $\leq 2.5$ mg/dL, creatinine level; $\leq$ upper limit of normal (ULN). The key exclusion criteria of study ADF30002 were subjects with hepatoma, autoimmune hepatitis, infection of hepatitis C virus or human immunodeficiency virus, serious complication, receiving/received anti-viral drugs, or pregnant women.		
	<b>From study ADF30002</b>	<b>From study 714LC-02</b>

<b>Number of Subjects:</b>			
Planned, N	35	35	
Entered, N	36	9	
Completed, n (%)	35(97)	9(100)	
Total Number Subjects Withdrawn, N (%)	1(3)	0	
Withdrawn due to Adverse Events n (%)	0	0	
Withdrawn due to Lack of Efficacy n (%)	0	0	
Withdrawn for other reasons n (%)	1(3)	0	
<b>Demographics</b>	<b>From study ADF30002</b>	<b>From study 714LC-02</b>	
N (All Subjects)	36	No summary available	
Females: Males	29:7		
Mean Age, years (SD)	44.0(9.38)		
Asian, n (%)	36(100)		
<b>Primary Efficacy Results: From study ADF30002</b>			
	(0-24W)	(0-48W)	0-84W
N(Efficacy:FAS)	35	34	34
Time-weighted change in log <sub>10</sub> HBV DNA from baseline up to 24 weeks, 48 weeks and 84 weeks (DAVG <sub>24</sub> , DAVG <sub>48</sub> and DAVG <sub>84</sub> ) (log <sub>10</sub> copies/mL)	-3.37	-3.84	-4.17
95% Confidence Interval	-3.619,-3.122	-4.137,-3.541	-4.480,-3.861
Change in ALT level at 24, 48 and 84 weeks from baseline(U/L) (Median)	-72.0	-73.5	-75.5
95% Confidence Interval	-253.92,-102.53	-225.85,-101.21	-230.38,-106.56
<b>Secondary Outcome Variable(s): From study ADF30002</b>			
<b>Serologic Measures:</b>	(0-24W)	(0-48W)	0-84W
Proportion of subjects with HBeAg loss (%)	10.3	13.8	14.3
Proportion of subjects HBeAg seroconversion (%)	7.1	7.1	3.7
<b>Virologic Measures:</b>	0-24W	0-48W	0-84W
Proportion of subjects with serum HBV DNA < 400 copies/mL at each study visit (%)	29.4	50.0	48.5
<b>Liver Function Tests:</b>	(0-24W)	(0-48W)	0-84W
Proportion of subjects achieving normal serum ALT (%)	74.3	82.4	88.2
Time to onset of confirmed serum ALT normalization (week, median)	12		
95% confidence interval	10.0, 16.0		

<b>Safety Results:From study ADF30002</b>	
N(Safety:SP)	34
<b>Most Frequent Adverse Events – On-Therapy</b>	
Subjects with any AE(s), n (%)	33(97)
Nasopharyngitis	20(59)
CPK increase	15(44)
Urine β <sub>2</sub> microglobulin increase	12(35)
NAG increase	10(29)
Malaise	8(24)
Abdominal pain upper	6(18)
Headache	6(18)
Diarrhea NOS	5(15)
Cough	5(15)

AFP increased	4(12)
Nausea	4(12)
Abdominal distension NOS	4(12)
Constipation	4(12)
Arthralgia	4(12)
Back pain	4(12)
<b>Serious Adverse Events - On-Therapy</b>	
[One serious adverse event (calculus ureteric) occurred in nine subjects from study 714LC-02 who were excluded from safety analyses.]	
Subjects with non-fatal SAEs, n (%)	2 ( 5.9)
	<b>n (%) [related]</b>
Hepatic neoplasm malignant NOS	1 (2.9) [0]
Breast mass NOS	1 (2.9) [0]
Cartilage injury	1 (2.9) [0]
Subjects with fatal SAEs, n (%)	0

**Conclusion:**

Long-term concurrent administration of adefovir dipivoxil tablets (GW284873X) 10mg/day and lamivudine tablets 100mg/day was conducted in subjects with chronic hepatitis B (including those with cirrhosis) who have signs of clinical deterioration associated with the replication of YMDD variant HBV.

Continuous improvement of the levels of serum HBV-DNA (a virological marker) was obtained, along with the sustained improvement and normalization of ALT (a hepatic function marker) that demonstrated long-term efficacy of concurrent use of adefovir dipivoxil tablets and lamivudine tablets.

Adverse events were reported in 33 (97%) subjects, with the most frequently reported being nasopharyngitis, CPK increase, and NAG increase. Serious adverse events were reported in 2 (5.9%) subjects. No fatal SAEs were reported.

**Publications:**

No Publication

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