

<b>Study No.:</b> ADF30002	
<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	
<b>Rationale:</b> The purpose of this study was to determine the efficacy and safety of Adefovir dipivoxil 10mg tablet in combination with lamivudine 100mg administered once daily for 16 weeks in chronic hepatitis B patients with abnormal liver function due to YMDD variant virus replication. This study was done to obtain early approval of Adefovir dipivoxil as a therapeutic agent for patients with aggravated hepatitis B due to replication of mutant hepatitis B virus as a result of lamivudine therapy.	
<b>Phase:</b> III	
<b>Study Period:</b> February 2003 – August 2003	
<b>Study Design:</b> One arm, open-label, multi-centre study	
<b>Centres:</b> 16 centres (site with actual enrollment)	
<b>Indication:</b> Combination with lamivudine for improvement of virological markers and liver function in adult patients with chronic hepatitis B and hepatitis B-related cirrhosis who have shown evidence of abnormal liver function associated with persistent hepatitis B virus (HBV) replication while receiving lamivudine mono-therapy.	
<b>Treatment:</b> Subjects received adefovir dipivoxil (10 mg tablet, oral administration) and lamivudine (100 mg tablet, oral administration) once daily for 16 weeks.	
<b>Objectives:</b> To assess the efficacy, safety and pharmacokinetics of adefovir dipivoxil, in an uncontrolled open study in which adefovir dipivoxil 10mg tablets and lamivudine 100mg tablets were administered once daily for 16 weeks, in patients with chronic hepatitis B (including patients with type B liver cirrhosis) in whom replication of YMDD mutant virus was detected following lamivudine administration.	
<b>Primary Outcome/Efficacy Variable:</b> Change from baseline in log <sub>10</sub> HBV-DNA through 16 weeks t	
<b>Secondary Outcome/Efficacy Variable(s):</b> Efficacy: Liver function test: ALT Virological Measures: HBeAg/Ab Pharmacokinetics: Pharmacokinetic parameters of adefovir dipivoxil	
<b>Statistical Methods:</b> <Efficacy>: Efficacy analysis will be performed primarily in FAS, and then in PPS to obtain reference for evaluation of the stability of results. Change from baseline in serum HBV-DNA (DAVG <sub>16</sub> ) Difference between the weighted mean of serum HBV-DNA level at Week 16 window and baseline (DAVG <sub>16</sub> ) will be calculated, and its two-sided 95% confidence interval be estimated. <Pharmacokinetics>: Pharmacokinetic parameters are calculated from the plasma adefovir concentration-time data without the use of model.	
<b>Study Population:</b> A total 71 subjects were enrolled in the study, 36 subjects completed the study, and 35 subjects were withdrawn from the study. The 35 subjects withdrawn from the study were all withdrawn at screening because they did not meet eligibility criteria. None of the subjects were withdrawn during the treatment period. The 36 subjects who met the eligibility criteria entered the treatment period and completed the 16-week treatment and went on to the long-term administration study.	
<b>Number of Subjects:</b>	
Planned, N	35
Entered, N	36
Completed, n (%)	36 (100)
Total Number Subjects Withdrawn, N (%)	0

Withdrawn due to Adverse Events n (%)	0
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for other reasons n (%)	0
<b>Demographics</b>	
N (FAS)	36
Females: Males	7 : 29
Mean Age, years (SD)	44.0 (9.38)
Race, n (%)	Asian (100)
<b>Primary Efficacy Results</b>	
N (Efficacy: FAS)	36
Mean change from baseline in serum HBV DNA (DAVG <sub>16</sub> : log <sub>10</sub> copies/mL)	-3.02
95% Confidence Interval	-3.231, -2.805
<b>Secondary Efficacy Results</b>	
N (Efficacy: FAS)	36
Mean change from baseline in ALT (IU/L)	-173.1
95% Confidence Interval	-246.5, -99.7
<b>Pharmacokinetics</b>	
C <sub>max</sub> (ng/mL), N=11	20.1
95% Confidence Interval	17.9, 22.3
AUC <sub>0-24</sub> (hr ng/mL), N=10	231.5
95% Confidence Interval	207.4, 255.7
<b>Safety</b>	
<b>Most Frequent Adverse Events -On-Therapy</b>	<b>n (%)</b>
Subjects with any AE(s), n(%)	28 (78)
Nasopharyngitis	12 (33)
Beta-N-acetyl-D-glucosaminidase increased	5 (14)
Diarrhoea NOS	5 (14)
Malaise	5 (14)
Headache	5 (14)
Alpha <sub>1</sub> foetoprotein increased	4 (11)
Beta <sub>2</sub> microglobulin urine increased	4 (11)
Constipation	4 (11)
Blood creatine phosphokinase increased	3 (8.3)
Nausea	3 (8.3)
<b>Serious Adverse Events - On-Therapy</b>	
<b>n (%) [n considered by the investigator to be related to study medication]</b>	
Subjects with non-fatal SAEs, n (%)	0
Subjects with fatal SAEs, n (%)	0

**Conclusion:**

**Publications:** Tanikawa K, Kumada H, Sata M: Clinical efficacy of the treatment with combined adefovir dipivoxil tablet and lamivudine tablet in chronic hepatitis B patients (including type B liver cirrhosis) with liver function abnormalities due to YMDD mutant virus replication. Kan Tan Sui (Japanese journal, language: Japanese). 2005; 50: 193-211.

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