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Study No.: ADF 103814	
Title: An open label, multicenter phase IV study of adefovir dipivoxil in Korean patients with chronic hepatitis B (CHB)	
Rationale: Adefovir dipivoxil has recently been launched in Korea, but no Korean-specific clinical evaluation of adefovir dipivoxil treatment in patients with chronic hepatitis B has been performed. This study was designed to evaluate the effect of anti-HBV activity of adefovir dipivoxil in Korean patients with HBeAg-positive CHB.	
Phase: Phase IV	
Study Period: Dec. 2004-Apr. 2006 (Last subject last visit: 28 th , Apr, 2006)	
Study Design: Open label, single arm	
Centres: 5 centers in Korea	
Indication: Chronic Hepatitis B (CHB)	
Treatment: Eligible subjects received open label adefovir dipivoxil 10mg once daily, taken orally.	
Objectives: The primary study objective was to assess the antiviral effect of 12 weeks of adefovir dipivoxil treatment in Korean patients with chronic hepatitis B and compensated liver disease. The secondary study objectives were to assess the antiviral effect, clinical benefit and safety of 52 weeks of adefovir dipivoxil treatment.	
Primary Outcome/Efficacy Variable: Mean log ₁₀ reduction in serum HBV DNA level from baseline to Week 12	
Secondary Outcome/Efficacy Variable(s): 1) Proportion of patients achieving ALT normalization at Week 52 2) Proportion of patients achieving virological response (HBV DNA level ≤ 300 copies/mL) at Week 52 3) HBV DNA levels at each collection timepoint through Week 52 4) Proportion of patients with HBeAg loss, HBeAg seroconversion, HBsAg loss and HBsAg seroconversion at Week 52 5) Proportion of patients achieving ALT normalization at Week 12 6) Safety assessment with adverse events as well as incidence of laboratory abnormalities	
Statistical Methods: ITT definition: All subjects regardless of whether or not the subject completed the planned duration of the study were analyzed with no data exclusions. This was the primary population for all analyses of efficacy and safety. PP definition: All subjects in the ITT population excluding all subjects with major protocol violations. This was a secondary population for the analysis of key efficacy data. This was only presented if results were different to those for the ITT population. Wilcoxon signed rank test was used to analyze mean log ₁₀ reduction in HBV DNA from baseline to week 12. For additional analyses to compare log ₁₀ HBV DNA between baseline and each visit, Wilcoxon signed rank test was used. ANCOVA model, controlling for baseline HBV DNA log ₁₀ values as covariates were used for 12 weeks HBV DNA to examine the homogeneity of sites. For continuous variables, descriptive statistics (N, Mean, SD, Median, Min, Max) were presented. For categorical variables, percentages and 95% exact confidence intervals were presented.	
Study Population: Korean patients with chronic hepatitis B (CHB)	
Key Inclusion Criteria	
- Presence of HBsAg for at least 6 months (positive once at least 6 months prior to screening and at time of screening).	
- Presence of HBeAg at the time of screening.	
- Positive HBV DNA plasma assay with screening value ≥ 10 ⁵ copies/mL (Roche COBAS AMPLICOR HBV MONITOR Test, LLOD 300 copies/mL) at the time of screening (within 4 weeks of baseline).	
- Evidence of at least one elevated serum alanine aminotransferase (ALT) level greater than 2.0 times the upper limit of the normal range (ULN) in the previous 6 months and serum ALT levels greater than 2 times the ULN at screening visit	
	Adefovir Dipivoxil 10mg
Number of Subjects:	
Planned, N	100
Entered, N	104
Completed, n (%)	102 (98)
Total Number Subjects Withdrawn, N (%)	2 (2)

Withdrawn due to Adverse Events n (%)	0		
Withdrawn due to Lack of Efficacy n (%)	0		
Withdrawn for other reasons n (%)	2 (2)		
Demographics (Baseline)			
N (ITT)	104		
Males: Females	83:21		
Mean Age, years (SD)	35.3 (10.4)		
Korean, n (%)	104 (100)		
Primary Efficacy Results:			
HBV DNA reduction from baseline to week12	Adefovir Dipivoxil 10mg		
Mean Baseline (SD)	7.94 (1.66)		
Mean Week12 (SD)	4.56 (1.13)		
Difference between treatments (as appropriate to endpoint)	-3.39 (1.50)		
95% Confidence Interval	NA		
p-value	<0.001		
Secondary Outcome Variable(s):			
Proportion of subjects achieving ALT normalization¹ at week 52			
Visit	N	Number of subject	95% exact CI ²
Week 52	104	83 (80%)	(70.8%, 87.0%)
1) ALT normalization is defined as a value ≤ULN (upper limit of normal range) based on the set of subjects with ALT>ULN at baseline.			
2) CI : Confidence Interval			
Proportion of subjects achieving virological response¹ at week 52			
Visit	N	Number of subject	95% exact CI ²
Week 52	104	34 (33%)	(23.8%, 42.6%)
1) Virological response is defined as HBV DNA level<300 copies/ml			
2) CI : Confidence Interval			
HBV DNA levels at each collection timepoint through week 52			
Serum HBV DNA	Statistic		
(log₁₀ copies/mL)	N	Mean	SD
Screening	104	7.98	1.40
Baseline	104	7.94	1.66
Week 4	104	5.59	0.83
Week 8	104	4.96	0.99
Week 12	104	4.56	1.13
Week 20	104	3.97	1.13
Week 28	103	3.92	1.14
Week 36	103	3.78	1.15
Week 44	102	3.63	1.13
Week 52	101	3.66	1.18
Proportion of subjects with HBeAg loss, HBeAg seroconversion¹, HBsAg loss and HBsAg seroconversion² at week 52			
Visit	N	Number of subject	95% exact CI ³
Week 52	HBeAg loss	103	19 (18%) (11.5%, 27.3%)
	HBeAg seroconversion	103	10 (10%) (4.8%, 17.1%)
	HBsAg loss	104	0 (0%) (0.0%, 3.5%)
	HBsAg seroconversion	104	0 (0%) (0.0%, 3.5%)
1) HBeAg seroconversion is defined as HBeAg negative and anti-HBe Ab positive			
2) HBsAg seroconversion is defined as HBsAg negative and anti-HBs Ab positive			
3) HBeAg loss and HBeAg seroconversion of subject ID 128 in week 28 were treated as non-responder because the result of HBeAg and HBeAb was 'equivocal' and 'positive' respectively.			
Proportion of subjects achieving ALT normalization¹ at week 12			
Visit	N	Number of subject	95% exact CI ²
Week 52	104	50 (48%)	(38.2 %, 58.1 %)

Safety	Adefovir Dipivoxil 10mg
Most Frequent Adverse Events – On-Therapy	n (%)
Subjects with any AE(s), n(%)	43 (41)
Fatigue	9 (9)
Upper Respiratory tract infection	7 (7)
Nausea	4 (4)
Dyspepsia	3 (3)
Thirst	3 (3)
Blood creatinine phosphokinase increased	3 (3)
Arthralgia	3 (3)
Abdominal pain upper	2 (2)
Abdominal discomfort	2 (2)
Epigastric discomfort	2 (2)
Nasopharyngitis	2 (2)
Pruritus generalised	2 (2)
Headache	2 (2)
Lymphadenopathy	2 (2)
Anorexia	2 (2)
Serious Adverse Events - On-Therapy	
n (%) [n considered by the investigator to be related to study medication]	
	Adefovir Dipivoxil 10mg
Subjects with non-fatal SAEs, n (%)	2 (1.92 %)
Ascites	1 [0]
Gastric Cancer	1 [0]
Lymphadenopathy	
n (%) [number of subjects who had "related" events]	1 [0]
Subjects with fatal SAEs, n (%)	0 (0 %)

Conclusion:

Primary Endpoint: Results for log₁₀ reduction in HBV DNA from baseline to Week 12 showed that mean was -3.39 log₁₀ copies/mL and median was -2.99 log₁₀ copies/mL. Wilcoxon signed rank test showed that there was statistically significant mean log₁₀ reduction in HBV DNA from baseline to Week 12 (p<.0001).

Secondary Endpoints: The number (percent) of subjects achieving serum ALT normalization at Week 12 was 50 (48.1%) and 83 (79.8%) at Week 52. The number (percent) of subjects with HBV DNA level < 300 copies/mL was 34 (32.7%) at week 52. At week 52, the number (percent) of subjects with HBeAg loss was 19 (18.4%) and with HBeAg seroconversion was 10 (9.7%) in 103 subjects. There were no subjects with HBsAg loss and HBsAg seroconversion at Week 12 and Week 52. Eighty-five AEs were reported by 43 of 104 subjects (41 %) Three SAEs (ascites, gastric cancer and lymphadenopathy) were reported in 2 subjects (2%). The events were judged by the investigator as not related to the study drug.

There were no fatal adverse events or AEs leading to discontinuation of the study drug.

Publications:

No Publication

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