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Study No.: ADF 108005
Title A phase IV, open label, single-arm, multi-centre, extension study of adefovir dipivoxil for Korean patients with chronic hepatitis B (CHB) who have completed ADF103814.
Rationale: Since lamivudine became available in Korea, the clinical experience with Korean patients showed that treatment with lamivudine was associated with a rapid and consistent suppression of HBV replication, significant improvement in liver histology, ALT normalization and enhanced rate of HBeAg loss and seroconversion. It also showed that long term use of lamivudine had been associated with the development of HBV mutations (YMDD variant) with reduced sensitivity to lamivudine. Adefovir dipivoxil was developed as another choice for the treatment of CHB. Potent anti-HBV activity of adefovir dipivoxil was observed in global phase II and III studies. Korean-specific clinical evaluation of adefovir dipivoxil treatment in patients with CHB was performed in ADF103814, which was one year study. This study was designed to evaluate the long-term effect of adefovir dipivoxil in Korean patients with HBeAg-positive CHB.
Phase: phase IV
Study Period: May, 2006~Apr. 2008
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: To assess the clinical efficacy and safety of long term (up to 3 years) adefovir dipivoxil therapy in Korean compensated CHB patients
Primary Outcome/Efficacy Variable: Mean log ₁₀ reduction in serum HBV DNA level after 3 years of adefovir therapy.
Secondary Outcome/Efficacy Variable(s): <ul style="list-style-type: none"> • Proportion of patients achieving ALT normalization at Week 104 and Week 156 • Proportion of patients achieving virological response (HBV DNA level ≤ 300 copies/mL) at Week 104 and Week 156 • HBV DNA levels at Week 104 and Week 156 • Proportion of patients with HBeAg loss, HBeAg seroconversion, HBsAg loss and HBsAg seroconversion at Week 104 and Week 156 • Safety assessment: incidence of adverse event(AE)s 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 is to be presented only if the results are different from that of ITT population. Wilcoxon signed rank test for HBV DNA reduction from baseline to week 156 was conducted and

median was presented instead of mean. For continuous variables, descriptive statistics (N, Mean, SD, Median, Min, Max) was summarized and for categorical variables, proportion and 95% exact confidence interval were presented.

Study Population: Korean patients with chronic hepatitis B (CHB)

Key Inclusion Criteria

1. Subject who had completed ADF103814 and continued with adefovir dipivoxil treatment via prescription without interruption prior enrolment in this extension study.
2. Availability and willingness of subject to provide written informed consent.
- 3 Male or female; a female was eligible to enter and participate in this study if she is of:
 - non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who was pre-menarchal or post-menopausal); or,
 - child-bearing potential, but had a negative serum pregnancy test at enrolment to this extension study, and agreed to use contraceptive.

	Adefovir Dipivoxil 10mg
Number of Subjects:	
Planned, N	104
Entered, N	80
Completed, N (%)	74 (93)
Total Number of Subjects Withdrawn, N (%)	6 (7)
Withdrawn due to Adverse Events N (%)	0
Withdrawn due to Lack of Efficacy N (%)	0
Withdrawn for other reasons n (%)	6 (7)
Demographics (Baseline demographic data)	
N (ITT)	104
Males: Females	83:21
Mean Age, years (SD)	35.3 (10.4)
Korean, n (%)	104 (100)
Primary Efficacy Results:	
HBV DNA (log₁₀ copies/ml) reduction from baseline to week 156	
Mean Baseline (SD)	7.94 (1.66)
Mean Week 156 (SD)	3.89 (1.59)
Mean difference between baseline and week 156 (SD)	-4.16 (1.79)
95% Confidence Interval	NA
p-value	<0.001

Secondary Outcome Variable(s):

1) **Proportion of subjects achieving ALT normalization¹⁾ at week 104 & 156**

Visit	N	Number of subject	95% exact CI ²⁾
Week 104	77	63 (81.8%)	(71.4%, 89.7%)
Week 156	73	65 (89.0%)	(79.5%, 95.1%) 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

2) Proportion of subjects achieving virological response¹⁾ at week 104 & 156

Visit	N	Number of subject	95% exact CI ²⁾
Week 104	77	20 (26.0%)	(16.6%, 37.2%)
Week 156	73	24 (32.9%)	(23.8%, 42.6%)

Virological response is defined as HBV DNA level<300 copies/ml

2) CI : Confidence Interval

3) HBV DNA levels at each collection time point through week 104 & 156

Serum HBV DNA (log 10 copies/mL)	Statistic		
	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
Week 68	74	3.90	1.37
Week 80	73	3.79	1.36
Week 92	77	3.99	1.49
Week 104	77	3.97	1.44
Week 120	76	3.88	1.44
Week 132	78	3.93	1.51
Week 144	74	3.97	1.55
Week 156	73	3.89	1.59

4) Proportion of subjects with HBeAg loss, HBeAg seroconversion¹⁾, HBsAg loss and HBsAg seroconversion²⁾ at week 104 & 156

Visit		N	Number of subject	95% exact CI ³⁾
Week 104	HBeAg loss	78	23 (29.5%)	(19.7%, 40.9%)
	HBeAg seroconversion	78	6 (7.7%)	(2.9%, 16.0%)
	HBsAg loss	78	0 (0.0%)	-
	HBsAg seroconversion	78	0 (0.0%)	-
Week 156	HBeAg loss	73	27 (37.0%)	(26.0%, 49.1%)
	HBeAg seroconversion	73	12 (16.4%)	(8.8%, 27.0%)
	HBsAg loss	73	1 (1.4%)	(0.0%, 7.4%)
	HBsAg seroconversion	73	0 (0.0%)	-

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 regarded as a non-responder because the result of HBeAg and HBeAb was in 'greyzone' and 'positive' respectively.

Safety Result	Adefovir Dipivoxil 10mg
Most Frequent AEs – On-Therapy	N (%)
Subjects with any AE(s), N(%)	64 (61.54)

ALT elevation	11 (10.58)
AST elevation	8 (7.69)
Skin and subcutaneous tissue disorders	7 (6.73)
Nasopharyngitis	6 (5.77)
Headache	6 (5.77)
Infections and infestations	6 (5.77)
Arthralgia	5 (4.81)
Abdominal pain	4 (3.85)
Dyspepsia	4 (3.85)
Nausea	4 (3.85)
Serious AEs - On-Therapy	
N: number of subject who had event (%) [number of subjects who had "related" events]	
	Adefovir Dipivoxil 10mg
Subjects with non-fatal SAEs, N (%)	2 (1.92 %) [0]
<u>Subject # 048</u> Acute pancreatitis, Cholangitis, Cholecystitis, Pancreatic cancer (adenocarcinoma)	1 (0.96%) [0]
<u>Subject # 065</u> Nasal bone fracture	1 (0.96%) [0]
Subjects with fatal SAEs, N (%)	0 (0 %)

Conclusion:

Primary efficacy results for mean and median log 10 reduction of HBV DNA from baseline to week 156 were -4.16 and -4.31 log₁₀ copies/mL. The Wilcoxon signed rank test showed that there was statistically significant mean log 10 reduction in HBV DNA from baseline to week 156 (p<0.0001). The HBV DNA level tended to decline over time until 52 weeks, and then stayed stable.

As for secondary efficacy results, the number (%) of subjects with HBV DNA level < 300 copies/mL at week 156 was 24 (32.9%, 95 CI= (22.3%, 44.9%)) and the number (%) of subjects achieving serum ALT normalization at week 104 and week 156 was 63(81.8%) and 65 (89.0%), respectively.

One subject missed HBV DNA measurement at week 156. Among 73 subjects with week 156 data, HBeAg loss occurred in 27(37.0%) patients, HBeAg seroconversion occurred in 12 (16.4%) patients, and HBsAg loss occurred in 1 (1.4%) patient

Sixty-four (61.4%) experienced 166 AEs. Thirteen subjects (12.50%) had 20 AEs which had relationships with the study drug. The most frequent AE was "ALT increased" (6 subjects (5.77%)). The second was "AST increased" (5 subjects (4.81%)). The third was "Blood creatine phosphokinase increased" (3 subject (2.88%)), "Nausea" in "Gastrointestinal disorders" (2 subjects (1.92%)) was the fourth. Most adverse events (131) were mild. Twenty-nine events were moderate, and 6 severe.

There was no SAE related to the study drug or AE-caused death or discontinuation of the study drug. There were no significant abnormalities in clinical laboratory data, vital signs or physical examination.

Publications: To be determined

Examples of approved summaries can be found on the Clinical Trial Register accessible at GSK.com or directly at <http://ctr.gsk.co.uk/welcome.asp>