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Study No.: ADF108356
Title: A 1 year Multi-Center, Open-label, local Phase IV Study to demonstrate the efficacy and safety of Adefovir Dipivoxil tablets(10mg) in Chinese subjects with Chronic Hepatitis B.
Rationale: Adefovir dipivoxil has been demonstrated to suppress HBV replication, normalize ALT and improve liver histology in Chronic Hepatitis B patients. This trial is a phase IV study (Chinese SFDA regulatory commitment) to provide additional evaluations of the efficacy and safety of adefovir dipivoxil 10 mg once daily in Chinese subjects with compensated chronic hepatitis B. The 48-week open label treatment evaluates the short term efficacy and safety parameters, early emergence of any adefovir-related mutations in the HBV polymerase and to evaluate any potential changes in renal function.
Phase: IV
Study Period: 31 December 2006 - 9 September 2008
Study Design: The study was a multi-centre, open label study, evaluating the efficacy and safety of treatment with ADV 10 mg in Chinese patients with compensated chronic hepatitis B. All subjects received open label ADV 10 mg once daily for 48 weeks to evaluate efficacy and safety of 48 weeks of monotherapy. The primary endpoint is the proportion of subjects achieving HBV DNA (<1000cp/mL). 100 subjects at baseline and among them at least 50 subjects at week 48 in the HBeAg positive chronic hepatitis B patients underwent liver biopsy, respectively, to evaluate liver histological changes pre and post ADV treatment in HBeAg positive chronic hepatitis B patients.
Centres: 27 centres in China
Indication: HBeAg positive/negative compensated chronic hepatitis B
Treatment: ADV 10mg tablets once daily for 48 weeks.
Objectives: The objective of the study was to evaluate the efficacy and safety of adefovir dipivoxil (ADV) 10 mg once daily over a 48 week treatment period in Chinese subjects with chronic hepatitis B (CHB).
Primary Outcome/Efficacy Variable: Proportion of subjects achieving HBV DNA <1000cp/mL at week 48

Secondary Outcome/Efficacy Variable:

- The proportion of subgroup subjects who underwent 2 sequential liver biopsies with improvement in liver histology (≥ 2 point reduction in the Knodell necroinflammation score without worsening fibrosis) after 48-week treatment.
- Ranked assessment of liver histology in the subgroup subjects who underwent 2 sequential liver biopsies.
- Reduction of serum HBV DNA (log copy/ml) from baseline to week 48
- The proportion of subjects with ALT normalization (ALT measurements at or below the upper limit of normal after baseline value above the upper limit of normal) at week 48.
- The proportion of subjects with HBeAg loss and HBeAg seroconversion (HBeAg positive patients only) at week 48.
- Nature and frequency of Adverse events over a 48 week treatment period.
- Nature and frequency of ADV-associated resistance over a 48 week treatment period.

Other Outcome/Efficacy Variable(s):

NA.

Statistical Methods: The sample size for this study was based on exposure requirement of China SFDA regulation related to Phase IV clinical trial for I-type drug which is 2000 cases. As part of these Phase IV commitments a total of 1470 Chinese subjects with compensated chronic hepatitis B were enrolled into this study.

A target of 100 enrolled HBeAg positive subjects were to undergo liver biopsy at baseline, and of these 50 subjects to repeat a second liver biopsy at week 48. These figures were accepted by the Chinese Regulatory Authority.

For analysis of the efficacy endpoint at week 48, only the summary statistics are provided for the Efficacy Analyses. No statistical analysis was performed.

Study Population:

Subject aged 18-65 years with presence of HBsAg at the time of screening and for at least 6 months prior to screening. Positive HBV DNA plasma assay with screening value $\geq 10^6$ copies/mL for HBeAg positive patients and $\geq 10^4$ copies/mL for HBeAg negative patients (Roche COBAS AMPLICOR™ HBV MONITOR Test, LLOD ≤ 300 copies/mL) at the time of screening (within 2 weeks of baseline). Evidence of elevated serum ALT levels defined as serum ALT level greater than or equal to 2.0 times (inclusive) the upper limit of the normal range (ULN) in 6 months prior to screening.

Number of Subjects:	1470
Planned, N	1470
Completed, n (%)	1342(91.3%)
Total Number Subjects Withdrawn, n (%)	128(8.7%)
Withdrawn due to Adverse Events, n (%)	6 (0.4%)
Withdrawn due to consent withdrawal, n (%)	35(2.4%)
Withdrawn due to lost to follow up, n (%)	80(5.4%)
Withdrawn due to protocol violation, n (%)	7 (0.5%)

Demographics					
N (ITT)		1467			
Females: Males		1176:291			
Mean Age, years (SD)		31.5(9.8)			
Asian, n (%)		1467(100)			
Efficacy Outcome					
Primary Efficacy Outcome Variable(s):					
Proportion of subjects achieving HBV DNA <1000cp/mL at week 48 (ITT population)					
	HBeAg + at baseline	HBeAg at baseline	Total		
	N=1108	N=359	N 1467		
HBV DNA <1000cp/mL (%)	341/1108 (33.8%)	243/359 (75.5%)	584/1467 (43.8%)		
Second Efficacy Outcome Variable(s):					
Proportion of HBeAg positive subjects with histological improvement up to week 48 (ITT population)					
% N			Total		
			N 71		
Histological improvement			64.8% (46/71)		
Ranked assessment of liver histology in HBeAg positive subjects up to week 48 (ITT population)					
Mean Median Range	Baseline	Week 48	Improved N(%)	No changes N(%)	Worsened N(%)
Knodell score	7.7 8 (1,17)	5.2 4 (1,10)	51(71.8)	10(14.1)	10(14.1)
Necroinflammation score	6.3 7 (1,14)	3.6 3 (1,7)	50(70.4)	13(18.3)	8(11.3)
Fibrosis score	1.4 1 (0,4)	1.5 1 (0,3)	7(9.9)	54(76.1)	10(14.1)
Reduction of serum HBV DNA (log copy/ml) from baseline to week 48 (log10 copies/mL)					
Median Range	HBeAg + at baseline	HBeAg - at baseline	Total		
	N=1108	N=359	N=1467		
Median HBV DNA log10 copies/ml at baseline	9.0 (3.4, 11.9)	7.4 (2.5, 7.6)	8.8 (2.5, 11.9)		
Serum HBV DNA Reduction over time (log10 copies/mL) Week 24	-4.1 (-9.4, 2.8)	-4.3 (-9.0, 1.8)	-4.2 (-9.4, 2.8)		

Serum HBV DNA Reduction over time (log₁₀ copies/mL) Week 48	-4.6 (-9.4, 3.5)	-4.6 (-9.0, 1.6)	-4.6 (-9.4, 3.5)
Proportion of subjects with ALT normalization at week 48 (ITT population)			
N (%)	HBeAg + at baseline	HBeAg - at baseline	Total
	N=1108	N=359	N 1467
Week 12	499/1087 (45.9%)	219/348(62.9%)	718/1435 (50%)
Week 24	726/1073 (67.7%)	271/347(78.1%)	997/1420 (70.2%)
Week 36	794/1058 (75%)	265/342(77.5%)	1059/1400 (75.6%)
Week 48	780/1012 (77.1%)	258/323(79.9%)	1038/1335 (77.8%)
Proportion of subjects with HBeAg loss and HBeAg seroconversion up to week 48 (ITT population)			
(HBeAg positive patients only)			
N (%)	HBeAg + at baseline		
	N=1108		
HBeAg loss	289/1108 (26.1%)		
HBeAg seroconversion	151/1108 (13.6%)		
ADV Mutation up to week 48			
Sera were examined for ADV resistance mutations in study subjects who met the following protocol-defined criteria:			
<p>Subjects with a >1 log₁₀ increase in HBV DNA from week 24 to 48, or</p> <p>≥Subjects with an HBV DNA 5 log₀ copies/ml both at week 24 and week 48</p>			
	Pts. No.	ADV resistance mutation (No.)	
>1 log ₁₀ increase in HBV DNA from week 24 to 48	66*	7 (1 with A181V+N236T, 6 with N236T)	
HBV DNA ≥ 5 log ₁₀ copies/ml both at week 24 and week 48	362*	16 (1with A181V+N236T, 15 with N236T)	
* sera were examined from 404 subjects (rather than 428), due to 24 subjects appearing in both groups.			
Four subjects with ADV resistance mutation (1 with A181V+N236T, 3 with N236T) appeared in both group as they matched both mutation test criteria.			
Therefore up to week 48, ADV resistance mutations were identified in a total of 19 (1.4%) subjects (18 with N236T and 1 with N236T+ A181V) .			

Safety Results:**Most Frequent Adverse Events up to week 48 (Top 3 most common AE, including AEs >5%)**

N (%)	Total (N=1467)
Nasopharyngitis	86(5.9%)
Blood creatine phosphokinase MB increased	24(1.6%)
Upper respiratory tract infection	19(1.3%).

All the subjects experienced at least one drug-related AE

N (%)	Total (N=1467)
Blood and lymphatic system disorders	
Total	9(0.6)
Anaemia	1(0.1)
Leukopenia	1(0.1)
Neutropenia	2(0.1)
Thrombocytopenia	2(0.1)
Hypereosinophilic syndrome	3(0.2)
Gastrointestinal disorders	
Total	3(0.2)
Abdominal discomfort	1(0.1)
Diarrhoea	1(0.1)
Nausea	1(0.1)
General disorders and administration site conditions	
Total	2(0.1)
Asthenia	2(0.1)
Immune system disorders	
Total	1(0.1)
Henoch-Schonlein purpura	1(0.1)
Infections and infestations	
Total	3(0.2)
Hepatitis B	3(0.2)
Investigations	
Total	28(1.9)
Alanine aminotransferase increased	1(0.1)
Blood calcium decreased	1(0.1)
Blood creatine phosphokinase MB increased	20(1.4)
Neutrophil count decreased	1(0.1)
Platelet count decreased	1(0.1)
Prothrombin time prolonged	1(0.1)
Blood phosphorus decreased	2(0.1)
Urine bilirubin increased	1(0.1)
Nervous system disorders	
Total	1(0.1)
Hypoaesthesia	1(0.1)

Psychiatric disorders	
Total	1(0.1)
Insomnia	1(0.1)
Renal and urinary disorders	
Total	2(0.1)
Azotaemia	1(0.1)
Renal impairment	1(0.1)
Skin and subcutaneous tissue disorders	
Total	1(0.1)
Rash	1(0.1)
Serious Adverse Events up to week 48	
n (%) [n considered by the investigator to be related to study medication]	
N (%)	Total (N=1467)
Subjects with fatal SAEs, n (%)	0
Hepatobiliary disorders	
Total	1(0.1)
Hepatic mass	1(0.1)
Infections and infestations	
Total	7(0.5)
Hepatitis B	7(0.5)
Investigations	
Total	3(0.2)
Alanine aminotransferase increased	2(0.1)
Transaminases increased	1(0.1)
Musculoskeletal and connective tissue disorders	
Total	1(0.1)
Muscle mass	1(0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Total	3(0.2)
Hepatic neoplasm malignant	3(0.2)
Renal and urinary disorders	
Total	1(0.1)
Nephrolithiasis	1(0.1)
Reproductive system and breast disorders	
Total	2(0.1)
Breast cancer	1(0.1)
Ovarian cyst	1(0.1)
A total of 0.4% (6/1470) of subjects discontinued treatment due to AE up to week 48	
Hepato carcinoma	1
Primary Liver Cancer	1
Liver cancer	1
Breast cancer	1
Both lower extremities	1
Abdominal discomfort	1
Diarrhoea	1

A total of 5 subjects became pregnant up to week 48. Among of them, 4 subjects had an elective abortion, and 1 was lost to follow up.

Protocol-defined grade 3/4 laboratory toxicities occurring up to Week 48

The most common grade 3 or grade 4 laboratory toxicities during the 48-week study were ALT elevation (2.4%), Calcium abnormal, occurring in 1.4% of subjects. Other common grade 3 or grade 4 laboratory toxicities included Platelets increased (1.1%), Potassium abnormal (1.0%), CPK elevation (0.9%) and Bilirubin elevation (0.5%)

Up to week 48, a total of 9/1467 (0.6%) subjects experienced a >0.5mg/dL increase from baseline in serum creatinine, and of these in two cases this was confirmed by a second consecutive test.

Up to week 48, 0.2% (3/1467) of subjects experienced a reduction in serum phosphorous to <1.4 mg/dL, but none was confirmed by a second consecutive test.

Conclusion

- Treatment with ADV 10mg up to 48 weeks resulted in HBV DNA reduction and HBV DNA undetectability (<1000 copies/mL) in 75.5% and 33.8% of HBe antigen-negative and -positive subjects, respectively.
- Treatment with ADV 10mg up to 48 weeks resulted in serological, histological and biochemical responses in a proportion of compensated Chinese CHB subjects.
- Adefovir resistance mutations were rare
- Adefovir was safe and well tolerated during 48 weeks of therapy.