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Study No.: ADF106632
Title: A 2-year multi-centre, open-label, local phase IV study to demonstrate the efficacy and safety of adefovir dipivoxil tablets (10mg) in Chinese subjects with HBe antigen negative Chronic Hepatitis B.
Rationale: Adefovir dipivoxil has been demonstrated to suppress HBV replication, normalize ALT and improve liver histology in HBeAg negative Chronic Hepatitis B (CHB). 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 presumed precore mutant chronic HBV. The 104-week open label treatment allows an adequate time to evaluate the long term efficacy and safety parameters, the emergence of any adefovir-related mutations in the HBV polymerase, and to evaluate any potential changes in renal function.
Phase: IV
Study Period: 20 Jan. 2006 -17 Sep. 2008
Study Design: This is a 2-year multi-center, single arm and open-label study, evaluating the efficacy and safety with using adefovir dipivoxil in Chinese subjects with HBeAg negative chronic hepatitis B. In the 2-year open label study period, all enrolled subjects regardless of YMDD mutant HBV at baseline received open label ADV at a dose of 10mg orally once daily for 104 weeks. The primary endpoint is the proportion of subjects with HBV DNA undetectable at week 104. 100 subjects at baseline and at least 50 subjects at week 104 underwent liver biopsy, respectively, to evaluate liver histological changes pre and post ADV treatment. Liver biopsy at week 52 was optional for subjects who had liver biopsy at baseline.
Centres: 17 centres in China
Indication: HBeAg negative chronic hepatitis B
Treatment: ADV 10mg tablets once daily for 104 weeks.
Objectives: The primary objective of the study was to evaluate the efficacy and safety of ADV 10mg once daily over a 104 week treatment period in Chinese subjects with HBeAg negative chronic hepatitis B (CHB). The secondary objectives were to evaluate the impact of YMDD mutant HBV at baseline on the efficacy and safety of ADV 10mg once daily in Chinese subjects with HBeAg negative CHB, and to evaluate the nature and frequency of ADV associated resistance mutations over a 104 week treatment period.
Primary Outcome/Efficacy Variable: Proportion of subjects achieving HBV DNA undetectable at week 104
Secondary Outcome/Efficacy Variable: <ul style="list-style-type: none"> • Proportion of the subgroup of subjects with 2 sequential liver biopsies with improvement in liver histology (≥ 2 point reduction in the Knodell necroinflammatory score without worsening in fibrosis) after 104-week treatment • Ranked assessment of liver histology in the subgroup of subjects with 2 sequential liver biopsies after 104-week treatment • Change from baseline in serum HBV DNA, and HBV undetectable (HBV DNA level ≤ 300 copies/mL by Roche COBAS AMPLICOR HBV MONITOR Test) over time • 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 104 • 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) over time
- Proportion of subjects with HBsAg loss defined as decrease in HBsAg to undetectable levels at week 104 in subjects with positive (detectable) serum HBsAg at baseline
 - Proportion of subjects with HBsAg seroconversion defined as HBsAg loss and development of detectable levels of anti-HBsAb at week 104 in subjects with positive (detectable) serum HBsAg at baseline
 - Proportion of subjects achieving complete response (defined as HBV DNA level ≤ 300 copies/mL by Roche COBAS AMPLICOR HBV MONITOR Test and ALT normalized) for two consecutive visits at least 3 month apart at week 104 and over time
 - Time to protocol - defined complete response over a 104 week treatment period
 - Nature and frequency of adverse events, deaths, laboratory abnormalities, changes in serum creatinine and phosphorous over a 104 week treatment period
 - Nature and frequency of ADV-associated resistance over a 104 week treatment period

Other Outcome/Efficacy Variable(s):
NA.

Statistical Methods: A total of 500 patients (including certain numbers of evaluable subjects who had developed YMDD variant HBV at baseline) would be enrolled into this study mainly based on the requirements from the Chinese Regulatory Authority as an appropriate study population for this Phase 4 study.

A target of 100 enrolled subjects at 4 sites would undergo liver biopsy at the baseline, and 50 subjects repeated liver biopsy at week 104, and some subjects had optional liver biopsy at week 52 in between. These figures were accepted by the Chinese Regulatory Authority.

Data analyses were performed when all subjects finished 104 weeks of treatment. Analyses of all efficacy data were performed on the Intent-to-Treat population. All data collected on these subjects was used in the analyses.

Study Population:

Subject aged 18-65 years with presence of HBeAg negative and HBeAb positive at the time of screening and for at least 6 months prior to screening. Positive HBV DNA plasma assay with screening value $\geq 10^4$ copies/mL (Roche COBAS AMPLICOR™ HBV MONITOR Test, LLOD ≤ 300 copies/mL) at the time of screening (within 4 weeks before baseline). Evidence of elevated serum ALT levels defined as serum ALT level greater than or equal to 1.3 times (inclusive) the upper limit of the normal range (ULN) in the previous 6 months.

A total of 533 subjects (including evaluable subjects who have developed YMDD variant HBV) were enrolled into this study. Among them, 43 subjects withdraw from the study due to following reasons: adverse events (5 subjects), consent withdrawn (11 subjects), lost to follow up (22 subjects), protocol violation (3 subjects) and other (2 subjects).

Number of Subjects:	Total
Completed n(%)	533(100.0)
Total Number Subjects Withdrawn, n (%)	43(8.1)
Withdrawn due to adverse event	5(0.9)
Withdrawn due to consent withdrawal	11(2.1)
Withdrawn due to lost to follow up	22(4.1)
Withdrawn due to protocol violation	3(0.6)
Withdrawn due to other reasons	2(0.4)
Demographics	
N (ITT)	533
Females: Males	121:412
Mean Age, years (SD)	38.7(10.4)
Median HBV DNA (log ₁₀ copies/ml)	6.5
Median ALT	1.9xULN

Efficacy outcome:			
• Primary Outcome/Efficacy Variable:			
Proportion of subjects achieving HBV DNA undetectable at week 104 (ITT population)			
	YMDD (n=45)	Non-YMDD (n=488)	Total (n=533)
Positive n(%)	10/42(23.8)	75/446(16.8)	85/488(17.4)
Negative n(%)	32/42(76.2)	371/446(83.2)	403/488(82.6)
Missing data was not included			
• Secondary Outcome/Efficacy Variable:			

Ranked assessment of liver histology in the subjects with 2 sequential liver biopsies during the period of 104 weeks (ITT population)

	Liver biopsy at week 52 (N=34) n(%)	Liver biopsy at week 104 (N=17) n(%)	Total (N=51) n(%)
Improvement in liver histology			
improvement	14 (41.2)	7 (41.2)	21(41.2)
no change	14 (41.2)	3 (17.6)	17(33.3)
worsened	6 (17.6)	7 (41.2)	13(25.5)
Necroinflammatory activity			
improvement	17 (50.0)	11 (64.7)	28(54.9)
no change	15 (44.1)	6 (35.3)	21(41.2)
worsened	2 (5.9)	0 (0.0)	2(3.9)
Fibrosis			
improvement	9 (26.5)	2 (11.8)	11(21.6)
no change	19 (55.9)	8 (47.1)	27(52.9)
worsened	6 (17.6)	7 (41.2)	13(25.5)

Summary of liver histology score in the subjects with 2 sequential liver biopsies during the period of 104 weeks (ITT population)

	Liver biopsy at week 52 (N=34)			Liver biopsy at week 104 (N=17)		
	Baseline	Week 52	Change	Baseline	Week 104	Change
Over Knodell HAI score						
Mean(SD)	7.9(3.1)	5.9(2.9)	1.9(2.8)	8.0(3.8)	5.4(2.8)	2.6(3.1)
Median	8.0	6.0	2.0	8.0	5.0	1.5
Min~Max	3~14	2~12	-4~8	4~15	1~12	-2~8
Necroinflammatory activity						
Mean(SD)	6.0(2.6)	4.2(2.4)	1.8(2.4)	6.3(3.0)	3.2(2.0)	3.1(2.3)
Median	6.0	3.0	1.8	7.0	2.5	3.0
Min~Max	2~11	1~9	-2~7	3~12	1~8	-1~7
Fibrosis						
Mean(SD)	1.9(1.0)	1.8(1.0)	0.1(1.2)	1.6(0.9)	2.1(1.2)	-0.5(1.1)
Median	1.0	1.0	0.0	1.0	3.0	0.0
Min~Max	1~4	1~3	-2~2	1~3	0~4	-2~2

Change from baseline in HBV DNA over time (ITT population)

	YMDD (N=45)	Non-YMDD (N=488)	Total (N=533)
Median HBV DNA log10 copies/ml at baseline	6.0 (2.5, 9.0)	6.5 (2.5, 9.7)	6.5 (2.5, 9.7)
Median reduction of HBV DNA from baseline log10 copies/ml			
Week 13	-2.7 (-5.2, 0.9)	-3.2 (-7.0, 3.4)	-3.2 (-7.0, 3.4)
Week 26	-3.0 (-6.0, 0.0)	-3.5 (-7.1, 1.4)	-3.5 (-7.1, 1.4)
Week 39	-2.9 (-6.0, 0.3)	-3.65 (-7.2, 2.5)	-3.60 (-7.2, 2.5)
Week 52	-3.0 (-6.1, 0.0)	-3.60 (-7.2, 2.4)	-3.60 (-7.2, 2.4)
Week 65	-2.90 (-6.1, 2.5)	-3.70 (-7.2, 2.9)	-3.70 (-7.2, 2.9)
Week 78	-3.10 (-6.1, 0.0)	-3.80 (-7.2, 2.9)	-3.80 (-7.2, 2.9)

Proportion of subjects achieving HBV DNA undetectable over time (ITT population)

	YMDD (N=45)	Non-YMDD (N=488)	Total (N=533)
Week 13 n(%)	20/45 (44.4)	242/483 (50.1)	262/528 (49.6)
Week 26 n(%)	27/45 (60.0)	323/480 (67.3)	350/525 (66.7)
Week 39 n(%)	30/45 (66.7)	363/478 (75.9)	393/523 (75.1)
Week 52 n(%)	33/45 (73.3)	380/477 (79.7)	413/522 (79.1)
Week 65 n(%)	32/45 (71.1)	383/469 (81.7)	415/514 (80.7)
Week 78 n(%)	32/45 (71.1)	383/468 (81.8)	415/513 (80.9)
Week 91 n(%)	36/45 (80.0)	385/460 (83.7)	421/505 (83.4)
Week 104 n(%)	32/42 (76.2)	371/446 (83.2)	403/488 (82.6)

Missing data was not included

Proportion of subjects with ALT normalization at week 104 (ITT population)

	YMDD (N=45) n(%)	Non-YMDD (N=488) n(%)	Total (N=533) n(%)
N	37	398	435
No	11(29.7)	91(22.9)	102(23.4)
Yes	26(70.3)	307(77.1)	333(76.6)

Normal ALT at baseline was defined as missing data and replaced in screening value

Missing data was defined as non-responding.

Proportion of subjects with ALT normalization over time (ITT population)

	YMDD (N=45) n(%)	Non-YMDD (N=488) n(%)	Total (N=533) n(%)
Week 13	19/37(51.4%)	254/394(64.5%)	273/431(63.3%)
Week 26	25/37(67.6%)	295/391(75.4%)	320/428(74.8%)
Week 39	28/37(75.7%)	312/390(80.0%)	340/427(79.6%)
Week 52	25/37(67.6%)	314/388(80.9%)	339/425(79.8%)
Week 65	25/37(67.6%)	303/383(79.1%)	328/420(78.1%)
Week 78	30/37(81.1%)	309/380(81.3%)	339/417(81.3%)
Week 91	31/37(83.8%)	321/377(85.1%)	352/414(85.0%)
Week 104	26/34(76.5%)	307/366(83.9%)	333/400(83.3%)

Missing data was not included.

Proportion of subjects with HBsAg loss and HBsAg seroconversion

One patient (without YMDD at baseline) had HBsAg loss up to week 104. No patient had HBsAg seroconversion.

Proportion of subjects achieving complete response at week 104 (ITT population)

	YMDD (N=45)	Non-YMDD (N=488)	Total (N=533)
No n(%)	21(46.7)	186(38.1)	207(38.8)
Yes n(%)	24(53.3)	302(61.9)	326(61.2)

Missing data was defined as non-responding

Time to protocol-defined complete response over a 104 week treatment period

	YMDD (N=45)	Non-YMDD (N=488)	Total (N=533)
N	32	381	413
Mean(SD)	300.0(172.9)	301.8(144.8)	301.6(147.0)
Median	186.0	274.0	274.0
Min~Max	183~729	92~735	92~735

Safety Results:

Most Frequent Adverse Events up to week 104 (Top 10 most common AE, including AEs >5%).

Adverse events	YMDD (N=45)	Non-YMDD (N=488)	Total (N=533)
Nasopharyngitis	4(8.9)	34(7.0)	38(7.1)
Upper respiratory tract infection	(2.2)	11(2.3)	12(2.3)
Pyrexia	0(0.0)	11(2.3)	11(2.1)
Fatigue	1(2.2)	8(1.6)	9(1.7)
Diarrhoea	2(4.4)	6(1.2)	8(1.5)
Dizziness	1(2.2)	6(1.2)	7(1.3)
Nausea	1(2.2)	6(1.2)	7(1.3)
Headache	0(0.0)	6(1.2)	6(1.1)
Cough	1(2.2)	5(1.0)	6(1.1)
Abdominal pain upper	0(0.0)	5(1.0)	5(0.9)

At least one drug-related Adverse Events up to week 104

Adverse events	YMDD (N=45)	Non-YMDD (N=488)	Total (N=533)
Gastrointestinal disorders	1(2.2)	5(1.0)	6(1.1)
Nausea	1(2.2)	4(0.8)	5(0.9)
Abdominal discomfort	0(0.0)	1(0.2)	1(0.2)
Diarrhoea	1(2.2)	0(0.0)	1(0.2)
General disorders and administration site conditions	0(0.0)	4(0.8)	4(0.8)
Fatigue	0(0.0)	3(0.6)	3(0.6)
Chest discomfort	0(0.0)	1(0.2)	1(0.2)
Investigations	0(0.0)	5(1.0)	5(0.9)
Blood creatine phosphokinase MB increased	0(0.0)	3(0.6)	3(0.6)
Creatinine renal clearance decreased	0(0.0)	3(0.6)	3(0.6)
Eosinophil count increased	0(0.0)	1(0.2)	1(0.2)
Metabolism and nutrition disorders	0(0.0)	1(0.2)	1(0.2)
Decreased appetite	0(0.0)	1(0.2)	1(0.2)
Skin and subcutaneous tissue disorders	0(0.0)	5(1.0)	5(0.9)
Alopecia	0(0.0)	3(0.6)	3(0.6)
Rash	0(0.0)	2(0.4)	2(0.4)
Pruritus	0(0.0)	1(0.2)	1(0.2)
Vascular disorders	1(2.2)	2(0.4)	3(0.6)
Dizziness	1(2.2)	1(0.2)	2(0.4)
Hypertension	0(0.0)	1(0.2)	1(0.2)

Serious Adverse Events up to week 104

Serious Adverse Events	YMDD (N=45)	Non-YMDD (N=488)	Total (N=533)
Infections and infestations	0(0.0)	1(0.2)	1(0.2)
Hepatitis B	0(0.0)	1(0.2)	1(0.2)
Investigations	0(0.0)	1(0.2)	1(0.2)
Alanine aminotransferase increased ¹	0(0.0)	1(0.2)	1(0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0(0.0)	1(0.2)	1(0.2)
Hepatic neoplasm malignant ²	0(0.0)	1(0.2)	1(0.2)
Nervous system disorders	0(0.0)	1(0.2)	1(0.2)
Neurilemmoma	0(0.0)	1(0.2)	1(0.2)
Respiratory, thoracic and mediastinal disorders	0(0.0)	1(0.2)	1(0.2)
Bronchitis chronic	0(0.0)	1(0.2)	1(0.2)
Vascular disorders	0(0.0)	1(0.2)	1(0.2)
Cerebral haemorrhage	0(0.0)	1(0.2)	1(0.2)

^{1,2} 551 subjects experienced 2 SAEs.

Subjects discontinued treatment due to AE up to week 104.

N (%)	YMDD (N=45)	Non-YMDD (N=488)	Total (N=533)
Subjects discontinued treatment due to AE	0	5(2.1%)	1(0.2)
Cerebral haemorrhage	0	1 59 subjects	1
Toe fracture	0	1 455 subjects	1
Hepatic neoplasm malignant	0	1 551 subjects	1
Neurilemmoma	0	1 569 subjects	1
Hepatitis B	0	1 718 subjects	1

No SAEs was considered by the investigators to be attributable to study medication.

There was no fatal event up to Week 104.

A total of 4 subjects became pregnant up to week 104. Of these, 2 subjects had an elective abortion, and 2 subjects delivered normal babies.

Protocol-defined grade 3/4 laboratory toxicities occurring up to Week 104

Laboratory parameter	3 or 4 grade			4 grade		
	YMDD (N=45)	Non-YMDD (N=488)	Total (N=533)	YMDD (N=533)	Non-YMDD (N=488)	Total (N=533)
Platelets	1(2.2)	11(2.3)	12(2.3)	0(0.0)	3(0.6)	3(0.6)
Calcium	1(2.2)	11(2.3)	12(2.3)	1(2.2)	3(0.6)	4(0.8)
CPK	1(2.2)	8(1.6)	9(1.7)	0(0.0)	3(0.6)	3(0.6)
Totalbilirubi	0(0.0)	7(1.4)	7(1.3)	0(0.0)	0(0.0)	0(0.0)
n						
ALT(SGPT)	0(0.0)	4(0.8)	4(0.8)	0(0.0)	1(0.2)	1(0.2)
Prothrombin Time	0(0.0)	4(0.8)	4(0.8)	0(0.0)	0(0.0)	0(0.0)
Potassium	1(2.2)	2(0.4)	3(0.6)	0(0.0)	1(0.2)	1(0.2)
AST(SGOT)	0(0.0)	3(0.6)	3(0.6)	0(0.0)	0(0.0)	0(0.0)
Hemoglobin	0(0.0)	2(0.4)	2(0.4)	0(0.0)	1(0.2)	1(0.2)
Amylase	0(0.0)	2(0.4)	2(0.4)	0(0.0)	0(0.0)	0(0.0)
Neutrophils	0(0.0)	1(0.2)	1(0.2)	0(0.0)	1(0.2)	1(0.2)
BUN	0(0.0)	1(0.2)	1(0.2)	0(0.0)	0(0.0)	0(0.0)

Up to week 104, a total of 7/533 (1.3%) subjects experienced a >0.5mg/dL increase from baseline in serum creatinine, but none was confirmed by a second consecutive test.

Up to week 104, 0.6% (3/533) of subjects experienced a reduction in serum phosphorous to <1.4 mg/dL, but none was confirmed by a second consecutive test.

ADV resistance mutation:

Up to week 52, ADV resistance mutations were identified in <1% (3/533) of subjects (2 with N236T and 1 with A181V) from available sera of subjects (n=32) with HBV DNA breakthrough (increase in HBV DNA level by 1 log₁₀ copies/ml or more from the treatment nadir) during 0-52 weeks.

Up to week 104, ADV resistance mutations were identified in 1.7% (9/533) of subjects (6 had N236T, 1 had A181V, and 2 had both) from available sera of subjects (n=77) with HBV DNA breakthrough (increase in HBV DNA level by 1 log₁₀ copies/ml or more from the treatment nadir) during 0-104 weeks.

Conclusion

The study results demonstrated that in patients with HBeAg-negative Chinese CHB, two years of ADV 10 mg daily treatment resulted in sustained histological, virologic and biochemical improvement.

Resistance associated mutations (N236T, A181V) were identified in 9 (1.7%) subjects out to 2 years.

The presence of YMDD mutant HBV DNA at baseline had no demonstrable impact on the efficacy and safety parameters.