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Study No.: ADF30001 (Year 1 to Year 5)
Title: A Multi-Center, Double-Blind , Randomized, Placebo-Controlled Phase II/III Study of Adefovir Dipivoxil for the Treatment of Chinese Patients with HBeAg positive Chronic Hepatitis B Followed by Long-term (5 Years total) Adefovir Dipivoxil Treatment. (Report on data out to 5 years)
Rationale: Adefovir dipivoxil (ADV) is a potent inhibitor of hepatitis B virus replication associated with HBeAg seroconversion and ALT normalisation. This study is designed to evaluate the efficacy and safety of 10 mg ADV tablets in the Chinese population, as regulatory requirement for marketing approval in China.
Phase: II/III
Study Period: 04 December 2002 -27 March 2008
<p>Study Design: This is a five year multi-centre study consisting of an initial one year randomized, double blind, placebo controlled study period followed by 4 years open label monotherapy:</p> <p><u>The first study phase (1st double-blind):</u> The first double-blind, randomised, placebo-controlled phase comparing ADV 10mg taken once daily with matching placebo taken once daily for 12 weeks. During this double-blind treatment period, subjects were randomised to receive either ADV 10 mg or placebo in a 3:1 ratio</p> <p><u>The second study phase (Open-label):</u> Following the first 12 week double-blind treatment period, all subjects in both ADV group and placebo group received open label ADV 10 mg once daily for 28 weeks to evaluate efficacy and safety of a further 28 weeks of monotherapy.</p> <p><u>The third study phase (2nd double-blind):</u> After completing a 40-week treatment period, subjects in the initial ADV group were re-randomised to receive either ADV 10 mg or placebo in a 2:1 ratio for 12 weeks to investigate response following continuous treatment or temporarily interrupted treatment. If the subjects experience liver disease progression during this period, open label ADV 10mg treatment was provided.</p> <p><u>The fourth study phase:</u> After completing the second double-blind treatment period (i.e. completion of 52 weeks of study treatment), all the subjects who remain in the study will be provided open label ADV 10 mg treatment for further 208 weeks (4 years). The long term efficacy and safety of this monotherapy will be evaluated.</p>
Centres: 12 centres in China
Indication: Chronic Hepatitis B HBeAg positive subjects
Treatment: ADV 10mg tablets or matched placebo once daily for 52 weeks, followed by 208

weeks ADV open label treatment. This report summarizes the five year (0-260 week) study results.

Objectives: The primary objective of the study was to assess antiviral activity, clinical benefit and safety of adefovir dipivoxil (ADV) 10 mg in Chinese patients with HBeAg positive chronic hepatitis B (CHB) at the end of Week 52 treatment. An additional study objective was to evaluate the long-term (5 years total) efficacy and safety of this monotherapy.

Primary Outcome/Efficacy Variable: Serum HBV DNA reduction from baseline to week 12

Secondary Outcome/Efficacy Variable: ALT normalisation at week 12 compared to baseline

Other Outcome/Efficacy and Safety Variable(s):

Over the 5 year treatment period:

- Reduction of serum HBV DNA
- The proportion of subjects with HBV DNA response defined as HBV DNA $\leq 10^5$ copies/mL or a $\geq 2 \log_{10}$ reduction from Baseline HBV DNA level
- The proportion of subjects with HBV DNA undetectable (<300 copies/mL)
- The proportion of subjects with ALT normalisation
- The proportion of subjects with HBeAg loss and HBeAg seroconversion
- The proportion of subjects developing N236T and A181V HBV DNA genotypic mutations associated with ADV resistance
- The safety outcome measures include all adverse events (AE), serious AEs (SAE), results of clinical laboratory tests, the laboratory toxicity grades and ALT elevations

Statistical Methods: The sample size for this study was based on the exposure requirement of China SFDA regulations related to new drug registration, rather than a formal sample size calculation based on the primary endpoint. This translates to at least 300 evaluable subjects on active drug and 100 evaluable subjects on placebo completing the phase II/III study.

A total of 480 subjects were enrolled, randomised between treatments in a 3:1 ratio, to provide greater than 95% power to detect a mean difference between ADV and placebo of 1.5 \log_{10} copies/mL for the week 12 change from baseline in \log_{10} copies/mL of HBV DNA.

For analysis of the primary endpoint, only subjects with non-missing serum HBV DNA value at baseline were included, using ANCOVA model, considering treatment and investigator as main effects; sex, age, baseline HBV DNA, and baseline ALT (/ULN) as the covariates. For the purposes of calculating the change from baseline, all values below LLOD were assumed to have a value assessed as the limit of detection. The statistical hypothesis was tested at two-side, alpha level equals to 0.05.

Chi-squared test was used to compare the proportion of subjects with ALT normalisation at Week 12 (ADV vs. PLA). ALT normalisation was defined as an ALT value $\leq 1.0x$ upper limit of the normal range for those subjects who had an abnormal ALT value ($>1.0x$ upper limit of the normal range) at baseline.

For analysis of the efficacy endpoint during week 0-260, only the summary statistics are provided for the Efficacy Analyses. No statistical analysis was performed. For the summary statistics that include data during week 0-260, the following three treatment groups were described:

Group AAAA: ADV(12 weeks) + OL-ADV(28 weeks) + ADV(12 weeks) + OL-ADV(52-260weeks)

Group AAPA: ADV(12 weeks) + OL-ADV(28 weeks) + PLA(12 weeks) + OL-ADV(52-260 weeks)
 Group PAAA: PLA(12 weeks) + OL-ADV(28 weeks) + ADV(12 weeks) + OL-ADV(52-260 weeks)

Study Population:

Subject aged 18-65 years with presence of HBsAg and HBeAg 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 (Roche COBAS AMPLICOR™ HBV MONITOR Test, LLOD < 300 copies/mL) at the time of screening (within 4 weeks of randomisation). 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 the previous 6 months., and serum ALT levels greater than 1.0 times the ULN at the time of screening

Number of Subjects:	PAAA	AAAA	AAPA
Planned, N	120	240	120
Randomised, N	120	240	120
Completed, n (%)	96(80%)	193 (80%)	101 (84%)
Total Number Subjects Withdrawn, n (%)	24 (20%)	47 (20%)	19 (16%)
Withdrawn due to Adverse Events, n (%)	2 (2%)	6(3%)	3 (3%)
Withdrawn due to consent withdrawal, n (%)	8(7%)	23 (10%)	10 (8%)
Withdrawn due to lost to follow up, n (%)	13(11%)	14 (6%)	6(5%)
Withdrawn due to protocol violation, n (%)	1 (1%)	2(1%)	0 (0%)
Withdrawn for other reasons, n (%)	0 (0%)	2(1%)	0(0%)
Demographics	PAAA	AAAA	AAPA
N (ITT)	120	240	120
Females: Males	22:98	39:201	22:98
Mean Age, years (SD)	32(10)	31(9)	32(10)
Asian, n (%)	120(100)	240(100)	120(100)
Efficacy Outcome			
Primary Efficacy Outcome Variable(s):			
Serum HBV DNA Reduction from baseline to week 12 (log₁₀ copies/mL)			
	PLA (n=120)	ADV (n=360)	
Mean Baseline (SD)	8.6 (10)	8.5 (10)	

Median of HBV DNA reduction at week 12 (mean ± SD)	-0.3 (1.2)	-3.3 (1.2)		
Range	- 5.2 to + 3.1	-7.7 to +0.5		
p-value	P < 0.001			
Second Efficacy Outcome Variable(s):				
Proportion of ALT normalisation at week 12 for subjects with elevated ALT at baseline				
	PLA (n=120)	ADV (n=360)		
Week 12 ALT normalisation (%)	15/108 (13.9%)	140/330 (42.4%)		
p-values	P < 0.001			
Other Efficacy Outcome Variable(s):				
Median Serum HBV DNA Reduction(log₁₀ copies/mL) up to week 260 compared to baseline				
	PAAA (N=120)	AAAA (N=240)	AAPA (N=120)	Combination of 3 groups N=480
Median Serum HBV DNA(log ₁₀ copies/mL) at Baseline(range)	8.8 (4.7, 11.1)	8.8 (4.5, 11.9)	8.8 (4.0, 11.1)	8.8 (4.0, 11.9)
Median of HBV DNA reduction at week 52 (range)	-5.0 (-8.0, 2.1)	-4.5 (-8.0, 0.7)	-0.2 (-6.1, 2.1)	-4.8* (-8.0, 2.1)
Median of HBV DNA reduction at week 104 (range)	-5.3 (-7.5, 2.3)	-5.0 (-8.0, 1.1)	-4.7 (-8.6, -0.3)	-5.0 (-8.6, 2.3)
Median of HBV DNA reduction at week 156 (range)	-5.2 (-7.6, 1.8)	-5.2 (-8.0, 0.9)	-4.9 (-6.8, -0.9)	-5.1 (-8.0, 1.8)
Median of HBV DNA reduction at week 208 (range)	-5.4 (-8.3, 2.1)	-5.4 (-8.0, 0.7)	-5.5 (-8.6, 1.0)	-5.4 (-8.6, 2.1)
Median of HBV DNA reduction at week 260 (range)	-5.5(-8.5, 2.0)	-5.6(-8.4, 0.2)	-5.3(-8.6, 0.2)	-5.5(-8.6, 2.0)
Proportion of subjects with serum HBV DNA responses up to week 260				
N (%)	PAAA (N=120)	AAAA (N=240)	AAPA (N=120)	Total (N=480)
Week 52 (response)	112/115 (97%)	218/231(94%))	25/115(22%)	330/346 (95%*)
Week 104(response)	105/112(94%))	199/218 (91%)	102/114(89%))	406/444 (91%)
Week 156(response)	103/111 (93%)	196/212(92%))	101/110(92%))	400/433 (92%)
Week 208(response)	97/104	178/201(89%)	96/106	371/411 (90%)

	(93%))	(91%)	
Week 260(response)	84/91(92%)	169/191(88%)	85/98(87%)	338/380(89%)
*serum HBV DNA response was defined as HBV DNA $\leq 10^5$ copies/mL or a $\geq 2 \log_{10}$ reduction from week 0 HBV DNA level				
*Only include group PAAA and AAAA which have received continuous ADV treatment, N=360				
Proportion of subjects with undetectable serum HBV DNA up to week 260				
N(%)	PAAA (N=120)	AAAA (N=240)	AAPA (N=120)	Total (N=480)
Subjects with HBV DNA <300 copies/mL at week 52	36/119 (30%)	67/236 (28%)	1/119 (1%)	103/355 (29%)*
Subjects with HBV DNA <300 copies/mL at week 104	52/116 (45%)	94/222 (42%)	48/118 (41%)	194/456 (43%)
Subjects with HBV DNA <300 copies/mL at week 156	48/115 (42%)	87/217 (40%)	45/114 (39%)	180/446 (40%)
Subjects with HBV DNA <300 copies/mL at week 208	56/108 (52%)	108/206 (52%)	55/109 (50%)	219/423 (52%)
Subjects with HBV DNA <300 copies/mL at week 260	50/95(53%)	113/194(58%)	53/101(52%)	216/390(55%)

Proportion of subjects with ALT normalization up to week 260 for subjects with elevated ALT at baseline				
	PAAA (N=120)	AAAA (N=240)	AAPA (N=120)	Total (N=480)
Week 52, N (%)	74/107 (69%)	176/224 (79%)	23/109 (21%)	250/331 (76%)*
Week 104, N(%)	80/105 (76%)	164/210 (78%)	77/108 (71%)	321/423 (76%)
Week 156, N(%)	80/103 (78%)	160/201(80%)	81/104 (78%)	321/408 (79%)
Week 208, N(%)	72/96 (75%)	148/194 (76%)	73/99 (74%)	293/389 (75%)
Week 260, N(%)	62/85(73%)	141/181(78%)	73/93(78%)	276/359(77%)
Proportion of subjects with HBeAg loss and HBeAg seroconversion up to week 260				
N (%)	PAAA (N=120)	AAAA (N=240)	AAPA (N=120)	Total (N=480)
Week 52				
HBeAg loss	24 /118(20%)	30 /233(13%)	10 /114(9%)	54/351 (15%)*
Seroconversion ¹	21/118(18%)	19/233(8%)	8/114(7%)	40/351 (11%)*
Week 104				
HBeAg loss	34/115(30%)	42/219(19%)	32/113(28%)	108/447

Seroconversion ¹	26/115(23%)	32/219(15%)	23/113(20%)	(24%) 81/447 (18%)
Week 156				
HBeAg loss	46/114 (40%)	69/212 (33%)	41/109 (38%)	156/435
Seroconversion ¹	34/114 (30%)	42/212 (20%)	25/109(23%)	(36%) 101/435 (23%)
Week 208				
HBeAg loss	48/106 (45%)	80/202 (40%)	45/105 (43%)	173/413
Seroconversion ¹	31/106 (29%)	43/202 (21%)	26/105 (25%)	(42%) 100/413 (24%)
Week 260				
HBeAg loss	50/95(53%)	94/191(49%)	46/97(47%)	190/383(50%)
Seroconversion ¹	32/95(34%)	55/191(29%)	25/97(26%)) 112/383(29%))
¹ . Defined as a decrease in HBeAg to undetectable an level and a rise in HBeAb to a detectable level				
ADV Mutation up to week 260				
Up to week 52, no ADV resistance mutations were identified out of 45 subjects with HBV DNA breakthrough (increase in HBV DNA level by 1 log ₁₀ copies/mL or more from the treatment nadir) during 0-52 weeks.				
Up to week 104, ADV resistance mutations were identified in 1.3% (6/480) of the subjects (3 with N236T and 3 with A181V) from available sera of subjects (n=137) with HBV DNA breakthrough during 0-104 weeks.				
Up to week 156, ADV resistance mutations were identified in 5.4% (26/480) of the subjects (12 had N236T, 12 had A181V, 1 had both, and one subject had N236T in the 2nd year but this was replaced by A181V in the 3rd year) from available sera of subjects (n=199) with HBV DNA breakthrough during 0-156 weeks.				
Up to week 208, ADV resistance mutations were identified in 10.4% (50/480) of the subjects (23 with N236T mutations and 20 with A181V mutations, 7 had both) from available sera of subjects (n=228) with HBV DNA breakthrough during 0-208 weeks.				
Up to week 260, ADV resistance mutations were identified in 14.6% (70/480) of the subjects (31 with N236T mutations and 29 with A181V mutations, 10 had both) from available sera of subjects (n=216) with HBV DNA breakthrough during 0-260 weeks.				
Safety Results:				
Most Frequent Adverse Events up to week 260 (Top 10 most common AE, including AEs >5%)				
N (%)	PAAA (N=120)	AAAA (N=240)	AAPA (N=120)	Total (N=480)

Upper respiratory tract infection	21 (18%)	33 (14%)	23 (19%)	77(16%)
Nasopharyngitis	16(13%)	30(13%)	13 (11%)	59(12%)
ALT increased	9 (8%)	12(5%)	15(13%)	36 (8%)
Hepatitis or Hepatitis B*	2(2%)	12(5%)	16(13%)	30(6%)
Fatigue	8 (7%)	9(4%)	10 (8%)	27(6%)
Diarrhea	1(1%)	13(5%)	6(5%)	20(4%)
Abdominal pain	2(2%)	9(4%)	4(3%)	15(3%)
Pyrexia	1 (1%)	9 (4%)	4 (3%)	14(3%)
Hepatic pain	5 (4%)	6 (3%)	3 (3%)	14(3%)
Rash	2 (2%)	8 (3%)	3(3%)	13(3%)

* The hepatitis or hepatitis B was originally reported by the investigators as "hepatitis B relapse, hepatitis B exacerbation or hepatitis B flare...However, they were coded (by data management) as hepatitis B or hepatitis for data analysis.

Serious Adverse Events up to week 260

n (%) [n considered by the investigator to be related to study medication]

	PAAA (N=120)	AAAA (N=240)	AAPA (N=120)	Total (N=480)
	n(%) [related]	n(%) [related]	n(%) [related]	n(%) [related]
Subjects with fatal SAEs, n (%)	2(1.6), [1]	1(0.8), [1]	0	3(0.6)
Gastric carcinoma	1(0.8), [0]	0	0	1(0.2)
Hepatic failure	0	1(0.8), [1]	0	1(0.2)
Acute hepatic failure	*1(0.8), [1]	0	0	1(0.2)
Hepatitis	*1(0.8), [1]	0	0	1(0.2)
Lung infection	*1(0.8), [0]	0	0	1(0.2)
Septic shock	*1(0.8), [0]	0	0	1(0.2)

*1 subject experienced 4 SAEs.

	n(%) related]	n(%) [relate d]	n(%) [relate d]	n(%) [related]
Subjects with non-fatal SAEs n (%)	4(3.3), [0]	12(5.0), [3]	10(8.3), [0]	26(5.4), [3]
Nasopharyngeal cancer	1*(0.8), [0]	0	0	1(0.2)
Hepatitis	1*(0.8), [0]	0	1(0.8), [0]	2(0.4)
Hepatitis B	1*(0.8), [0]	5(2.1), [2]	8*(6.7), [0]	14(2.9)
ALT elevation	0	3(1.3), [0]	0	3(0.6)
Spontaneous abortion	0	1(0.4), [1]	0	1(0.2)
Intestinal obstruction	0	1*(0.4), [0]	0	1(0.2)
Diabetes	0	1*(0.4), [0]	0	1(0.2)
Bronchial pneumonia	0	0	1*(0.8), [0]	1(0.2)
Liver carcinoma	0	0	1(0.8), [0]	1(0.2)
Cholelithiasis	0	1**(0.4), [0]	0	1(0.2)
Cholecystitis	0	1**(0.4), [0]	0	1(0.2)
Cellulitis	1(0.8), [0]	0	0	1(0.2)
Upper respiratory tract infection	*1(0.8), [0]	0	0	1(0.2)
Fracture	0	1(0.4), [0]	0	1(0.2)
Lower limb fracture	1(0.8), [0]	0	0	1(0.2)
Limb injury	0	0	1*(0.8), [0]	1(0.2)
Pelvic fracture	0	0	1(0.8), [0]	1(0.2)

Acute abdomen	0	1**(0.4), [0]	0	1(0.2)
* 6 of the subjects had experienced 2 SAEs. **1 of the subjects had experienced 3 SAEs.				
Protocol-defined grade 3/4 laboratory toxicities occurring up to Week 260				
The most common grade 3 or grade 4 laboratory toxicities during the five-year study were serum ALT elevation, occurring in 41% (199/480) of subjects across all three treatment groups. The majority of the ALT elevation toxicities occurred in the initial active treatment phase in the three treatment groups and following re-randomisation to PLA in the AAPA group. Other common grade 3 or grade 4 laboratory toxicities included neutrophils decrease (8%), CPK elevation (7%), bilirubin elevation (7%), platelet decrease (6%), and phosphorous decrease (2%).				
Conclusion See publication.				

Publications

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11. Yimin Mao, etc. Efficacy And Safety Of 4 yrs Adefovir Dipivoxil (ADV) 10mg In Chinese HBeAg+ve Chronic Hepatitis B (CHB). *Hepatology International* Volume 2, Number 1 March, 2008
12. Jinlin Hou, etc. Adefovir Dipivoxil (ADV)10mg Resistance at 4 yrs ADV In Chinese HBeAg+ve Chronic Hepatitis B (CHB). *Hepatology International* Volume 2, Number 1 March, 2008
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14. Y. M. Mao, M. D. Zeng etc. Efficacy and safety of 5 years uninterrupted adefovir dipivoxil 10mg (ADV) in Chinese HBeAg positive chronic hepatitis B (CHB). *Hepatology International* Volume 3 Number 1, March 2009
15. J. L. Hou, Y. Z. Wang etc. Adefovir dipivoxil 10mg (ADV) resistance at 5 yrs in Chinese HBeAg+ve chronic hepatitis B (CHB). *Hepatology International* Volume 3 Number 1, March 2009

