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Study No.: ADF30001 (Year 1 to Year 4)
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 4 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 February 2007
<p>Study Design: This is a one year randomised, multi-centre, double blind, placebo controlled study followed by 4 year open label monotherapy which includes four study phases.</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 to establish the controlled data in the primary endpoint.</p> <p><u>The second study phase (Open-label):</u> Following the 12 weeks of the first 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 mono-therapy.</p> <p><u>The third study phase (2nd double-blind):</u> After completing the 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 can be provided.</p> <p><u>The fourth study phase:</u> After completing the second double-blind treatment period (i.e. completion of the 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 mono-therapy will be evaluated.</p>
Centres: 12 centres in China
Indication: HBeAg positive chronic Hepatitis B
Treatment: ADV 10mg tablets or matched placebo once daily in 52 week treatment then followed by 208 weeks ADV open label treatment. This report summarises the first to third year (0-208 week) study results.
Objectives: This report presents data out to 4 years of this 5-year study. 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. Additional study objectives are 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 Variable(s):

- 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

Statistical Methods: The sample size for this study was based on exposure requirement of China SFDA regulations related to new drug registration, rather than formal sample size calculations based on the primary endpoint. At least 300 evaluable subjects on active drug and 100 evaluable subjects on placebo were required to complete the phase II/III study.

A total enrollment of 480 subjects, randomised between treatments in a 3:1 ratio, was expected 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.

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

For analysis of the efficacy endpoint during weeks 52-208, only the summary statistics are provided for the 'Efficacy Analyses'. No statistical analysis was performed. For the summary statistics that include data during weeks 52-208, the following three treatment groups were described:

Group AAAA: ADV(12 weeks) + OL-ADV(28 weeks) + ADV(12 weeks) + OL-ADV(52-208 weeks)

Group AAPA: ADV(12 weeks) + OL-ADV(28 weeks) + PLA(12 weeks) + OL-ADV(52-208 weeks)

Group PAAA: PLA(12 weeks) + OL-ADV(28 weeks) + ADV(12 weeks) + OL-ADV(52-208 weeks)

This report presents results for Year 1 to Year 4.

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 < 200 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

Completed, n (%)	108 (90)	205 (85)	108 (90)	
Total Number Subjects Withdrawn, n (%)	12 (10)	35 (15)	12 (10)	
Withdrawn due to Adverse Events, n (%)	2 (2)	5 (2)	1 (1)	
Withdrawn due to consent withdrawal, n (%)	4 (3)	19 (8)	8 (7)	
Withdrawn due to lost to follow up, n (%)	5 (4)	6 (3)	2(2)	
Withdrawn due to protocol violation, n (%)	0 (0)	1 (1)	0 (0)	
Withdrawn for other reasons, n (%)	1 (1)	4 (2)	1(1)	
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)	239 (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 (14)	140/330 (42)	
p-values		P < 0.001		
Other Efficacy Outcome Variable(s):				
Median Serum HBV DNA Reduction(log₁₀ copies/mL) up to week 208 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)	8.8 (4.7, 11.1)	8.8 (4.5, 11.9)	8.8 (4.0, 11.1)	8.8 (4.0, 11.9)

of Baseline (range)				
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)
*Only include groups PAAA and AAAAA which have received continuous ADV treatment, N=360				
Proportion of subjects with serum HBV DNA¹ responses up to week 208				
	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 (93)	178/201(89)	96/106 (91)	371/411 (90)
¹ 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 groups PAAA and AAAAA which have received continuous ADV treatment, N=360				
Proportion of subjects with undetectable serum HBV DNA up to week 208				
	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)
*Only include groups PAAA and AAAAA which have received continuous ADV treatment, N=360				
Proportion of subjects with ALT normalization up to week 208 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)
Proportion of subjects with HBeAg loss and HBeAg seroconversion up to week 208				
	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 (24)
Seroconversion ¹ (%)	26/115 (23)	32/219 (15)	23/113 (20)	81/447 (18)
Week 156				
HBeAg loss (%)	46/114 (40)	69/212 (33)	41/109 (38)	156/435 (36)
Seroconversion ¹ (%)	34/114 (30)	42/212 (20)	25/109 (23)	101/435 (23)
Week 208				
HBeAg loss (%)	48/106 (45)	80/202 (40)	45/105 (43)	173/413 (42)
Seroconversion ¹ (%)	31/106 (29)	43/202 (21)	26/105 (25)	100/413 (24)

¹Defined as a decrease in HBeAg to undetectable an level and a rise in HBeAb to a detectable level

*Only include groups PAAA and AAAAA which have received continuous ADV treatment, N=360.

ADV Mutation up to week 208

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 log₁₀ copies/mL or more from the treatment nadir) during the 0-52 week study.

Up to week 104, ADV resistance mutations were identified in 1.3% (6/480) of the subjects (3 with N236T and 3 with A181V) out of 137 subjects with HBV DNA breakthrough during the 0-104 week study.

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) out of 199 subjects with HBV DNA breakthrough during the 0-156 week study.

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) out of 228 subjects with HBV DNA breakthrough during the 0-208 week study.

Safety Results:

Most Frequent Adverse Events up to week 208 – on therapy

n(%)	PAAA (N=120)	AAAA (N=240)	AAPA (N=120)	Total (N=480)
Upper respiratory tract infection	21 (18)	34 (14)	20 (17)	75 (16)
Nasopharyngitis	15 (13)	24 (10)	6 (5)	45 (10)
Alanine aminotransferase increased	6 (5)	11 (5)	13 (11)	30 (6)
Hepatitis or Hepatitis B	2 (2)	9 (4)	15 (13)	2 (5)
Fatigue	8 (7)	8 (3)	10 (8)	26 (5)
Abdominal pain upper	3 (3)	12 (5)	7 (6)	22 (5)
Diarrhoea	5 (4)	9 (4)	13 (11)	16 (3)
Pyrexia	1 (<1%)	9 (4)	4 (3)	14 (3)
Hepatic pain	5 (4)	6 (3)	3 (3)	14 (3)
Cough	4 (3)	5 (2)	5 (4)	14 (3)

Serious Adverse Events up to week 208 – on-therapy

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 (%)	1(0.8), [0]	1(0.8), [1]	0	2(0.4)
Gastric carcinoma	1(0.8), [0]	0	0	1(0.2)
Hepatic failure	0	1(0.8), [1]	0	1(0.2)
	n(%) [related]	n(%) [related]	n(%) [related]	n(%) [related]
Subjects with non-fatal SAEs, n (%)	5 (4.2), [0]	11 (4.6),[1]	10(8.3), [0]	26(5.4)[1]
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]	3(1.3), [0]	7*(5.8), [0]	11(2.3)
ALT elevation	0	3(1.3), [0]	0	3(0.6)
Spontaneous abortion	0	2(0.8), [1]	0	2(0.4) [1]
Fracture	0	1(0.4), [0]	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)
Cellulitis	1(0.8), [0]	0	0	1(0.2)
Upper respiratory tract infection	1(0.8), [0]	0	0	1(0.2)
Lower limb fracture	0	0	1(0.8), [0]	1(0.2)
Pelvic fracture	1(0.8), [0]	0	0	1(0.2)

* One of the subjects experienced 2 SAEs.

Conclusion

At week 12 there was a statistically significant difference in the median log₁₀ HBV DNA reduction between subjects treated with PLA and ADV. In addition there was a statistically significant difference in the proportion of subjects with ALT normalisation between subjects treated with PLA and ADV at the same timepoint.

208 weeks of ADV therapy resulted in sustained virological, serological and biochemical responses in HBeAg positive Chinese CHB subjects.

Publications:

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