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ASSESSMENT REPORT
FOR
HEPSERA

International Nonproprietary Name:
Adefovir Dipivoxil

Procedure No. EMEA/H/C/485/II/30

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Introduction

Adefovir dipivoxil is an oral prodrug of adefovir, a phosphonate nucleotide analogue of adenosine monophosphate which is an inhibitor of hepatitis B virus (HBV) replication *in vitro* and *in vivo*.

Hepsera (adefovir dipivoxil) 10 mg tablets in a once daily regimen is currently approved for the treatment of chronic hepatitis B in adults with compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and fibrosis, or decompensated liver disease.

The Marketing Authorisation Holder (MAH) applied for an extension of the therapeutic indication for Hepsera to include adolescent patients aged 12 to 17 years with compensated liver disease, evidence of active viral replication and persistently elevated serum ALT levels.

The Hepatitis B Virus (HBV) infection in children is generally characterised by a more benign disease as compared to adults, with only some children having an active disease that might require an early treatment introduction.

The risk of developing chronic HBV infection ranges from 90% in newborn of HbeAg positive mothers, to 20-30% in infants and children infected during the first 5 years of life, to 6-10% in children infected after 6 years of age. Long-term follow-up studies in children have shown that more than 80% seroconverted from HBeAg to anti-HBe before reaching adulthood.

In spite of a more benign course of the disease in comparison to adult, the long-term complications of chronic HBV (i.e. cirrhosis and hepatocellular carcinoma - HCC) have also been found in children, although infrequently. Furthermore, patients with ongoing viral replication that acquired chronic HBV early in life are at highest risk for development of progressive liver disease, cirrhosis and HCC.

Despite well established guidelines for the treatment of chronic Hepatitis B (CHB) in adult patients, there is less consensus on when to start treatment in paediatric patients. Initiating treatment in children should be carefully weighed to avoid promoting an early introduction of treatment in the paediatric population that could lead to the exhaustion of therapy in this population through the risk of emergence of resistance. At present, no antiviral medicinal product has been approved in the European Union for the treatment of chronic hepatitis B in the paediatric population.

In support of this type II variation to extend the therapeutic indication to adolescent, a main efficacy and safety study (GS-US-103-518), two bioequivalence studies for the investigational adefovir oral suspension formulations (formulation A study GS-02-515; and formulation B study GS-02-536) and a dose finding pharmacokinetic study (GS-02-517, formulation A) were submitted.

Data from these studies concern all paediatric age groups and not only the applied age range of 12 to <18 years. All submitted studies have previously been assessed by the CHMP in the setting of Hepsera follow-up measures.

Clinical aspects

The clinical paediatric development program for adefovir dipivoxil included three completed pharmacology studies and an ongoing paediatric efficacy and safety study. During the development program, two investigational oral suspension formulations of adefovir were evaluated, A and B (only different in taste).

- Main study: *GS-US-103-518*, initial 48 week efficacy and safety data of this double blind placebo controlled study in chronic hepatitis B paediatric patients aged 2 – 17 years old using oral suspension B and the 10 mg tablet formulation. The open-label phase of this study is currently ongoing;

- Supportive studies: *GS-02-515*, bioequivalence of adefovir dipivoxil oral suspension A with the marketed 10 mg tablet;

  GS-02-517, a pharmacokinetic study using oral suspension A to identify the adefovir dipivoxil doses to evaluate the efficacy and safety in chronic hepatitis B paediatric patients (in study GS-US-103-518);

  GS-02-536, bioequivalence of adefovir dipivoxil oral suspension B with the marketed 10 mg tablet;

Clinical pharmacology

Pharmacokinetics

Bioequivalence studies

Studies GS-02-515 and GS-02-536

These studies were phase I, open-label, randomised, crossover studies in which healthy adult subjects were to receive a single 10 mg (5 ml) dose of adefovir dipivoxil suspension formulation A (study GS-02-515) or adefovir dipivoxil suspension formulation B (study GS-02-536), and in a separate study period, a single 10 mg adefovir dipivoxil tablet. There was a 7-day washout period.

Twenty-four subjects enrolled in study -515 and 22 completed the study. In study -536 twenty were enrolled, and 17 completed the study.

In both studies, the 90% confidence intervals (CIs) for the geometric mean ratios of the oral suspension formulations/tablet AUC_{inf}, $AUC_{0\text{-}last}$, and C_{max} were within the range of 80% to 125%, demonstrating that both adefovir dipivoxil suspension formulation A and formulation B and the tablet formulation were bioequivalent. No safety concerns arose from these studies.

Dose selection study

Study GS-02-517

This was a multicentre, phase I-II, open-label study to determine a dosage regimen for each paediatric group (2-17 years) that would produce adefovir plasma exposures similar to that of adults receiving the approved dose of 10 mg once daily (in study GS-00-472).

Two different doses were assessed in the 2–6 years and 7–11 years age groups, one dose of 0.14 mg/kg and one dose of 0.3 mg/kg with a 7-day washout period. Subjects 12–17 years of age received a single dose of 10 mg oral suspension formulation.

Population

Children and adolescents with chronic hepatitis B and compensated liver disease, HbeAg positive, aged 2 to 17 years old, with serum hepatitis B virus (HBV) DNA ≥ 105 copies/ml, and creatinine clearance ≥ 80 ml/min.

Forty-seven patients were enrolled, 2 discontinued before receiving study medication. Data of 45 patients were analysed (12 aged 2-6 years, 18 aged 7-11 years and 15 aged 12-17 years).

Pharmacokinetic results

The adefovir exposure from the 10 mg dose in adolescents 12 – 17 years of age was similar to those observed in adults. In adolescents, mean C_{max} and $AUC_{0\text{-}inf}$ were respectively 22.8 ng/ml and 237.3 ng.hr/ml compared to 18.4 ng/ml and 220.3 ng.hr/ml in adult patients with chronic hepatitis B (study GS-00-472).

In the age range 2-6 years and 7-11 years, the $AUC_{o\text{-}t}$, $AUC_{o\text{-}inf}$ and C_{max} mean values following a 0.14 mg/kg dose of adefovir dipivoxil were much lower (40 to 60 %) than in the targeted adult values.

In the age range 2-6 years, the $AUC_{o\text{-}t}$, $AUC_{o\text{-}inf}$ mean values following a 0.3 mg/kg dose of adefovir dipivoxil were comparable to adults whereas the mean C_{max} was 46 % higher than the adult values.

In the 7–11 years of age group, $AUC_{o\text{-}t}$, $AUC_{o\text{-}inf}$ mean values were approximately 25 % higher than the adult exposure values and C_{max} mean values are 80% higher than the adult values.

Based on these results, the following dosing recommendations for adefovir dipivoxil in paediatric patients were agreed:

- patients aged 12-17 years old: 10 mg/day;
- patients aged 2 to 6 years old: 0.3 mg/kg (up to 10mg/day);
- patients aged 7 to 11 years old: 0.25 mg/kg (the 0.3 mg/kg resulted in a C_{max} and $AUC_{0\text{-}\infty}$ higher than those achieved in adults. Assuming linear pharmacokinetics, a dose of 0.25 mg/kg appeared to provide a C_{max} and $AUC_{0\text{-}\infty}$ closer to the adult target dose - C_{max} 25.74 ng/ml, $AUC_{0\text{-}\infty}$ 227.74 ng.hr/ml).

Main study' pharmacokinetics

Study GS-US-103-518

This was a phase III, efficacy and safety study in paediatric subjects with CHB. Subjects were randomised to adefovir dipivoxil or placebo (2:1 ratio), with stratification by age at the first dose (2−6, 7−11, 12−17 years, inclusive) and by CHB treatment history (prior treatment, no prior treatment). Formulation and daily dose were based on age and weight (daily dose not to exceed 10 mg).

Pharmacokinetic results

Adefovir pharmacokinetic parameters from paediatric patients (GS-US-103-0518) and adult patients (GS-00-472) are summarised hereafter:

Study Age Group	Pharmacokinetic parameter	
	Cmax (ng/ml)	**AUCtau (ng•h/ml)**
GS-US-103-518		
2-6 years (0.3 mg/Kg suspension)	17.09	210.37
7-11 years (0.25 mg/Kg suspension)	18.47	222.09
12-17 years (10 mg tablets)	21.96	248.76
GS-00-472		
Adults (10 mg tablet)	19.71 (8.15)	215.75 (78.61)

Although a slight increase in AUC and C_{max} was observed for the older children, adefovir plasma exposure was similar among the three paediatric age groups.

Discussion and conclusion on pharmacokinetics

The selected doses for study GS-US-103-518 were well documented and bioequivalence between tablets and oral suspension formulations was shown in studies GS-02-515 and GS-02-536.

The adefovir dipivoxil dosing regimens used in paediatric patients in study GS-US-103-518 were adequate from a pharmacokinetic point of view. Adefovir plasma concentrations were comparable in the three paediatric age groups, and each age group achieved the target adefovir concentrations reported in adult CHB patients.

These studies were however, of secondary importance since the MAH requested to extend the indication to children above 12 years of age for which the already approved 10 mg tablet formulation is adequate.

Clinical efficacy

Study GS-US-103-518

This was a phase III, multicentre study to investigate the efficacy and safety of adefovir dipivoxil (ADV) in HbeAg positive treatment-naïve and treatment-experienced children and adolescents with compensated liver disease following 48 weeks of treatment. The open-label phase of this study is currently ongoing. The two study treatment periods are:

- Weeks 0-48: randomised (2:1 ratio), double-blind, placebo-controlled, parallel-group; randomisation stratified by age at the first dose of study treatment (2 to < 7 years; ≥ 7 to < 12 years; ≥ 12 to < 18 years) and prior treatment for CHB (prior treatment; no prior treatment).
- Weeks 49–240: open-label for all placebo treated subjects not exhibiting HBeAg or HBsAg seroconversion at week 44 and for all others ADV treated patients who were eligible to continued treatment for up an additional 192 weeks.

Population

Treatment- naïve and treatment-experienced paediatric subjects (age 2 < 18 years) with evidence of active disease, HbsAg positive for at least 6 months and HbeAg positive, with serum HBV DNA ≥ 10^5 copies/ml.

Serum ALT levels ≥ 1.5 upper limit of normal (ULN) at both initial and confirmatory screening visits, compensated liver disease, and creatinine clearance ≥ 80 ml/min.

Patients were to be seronegative for Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV) and Hepatitis D Virus (HDV).

Subjects from the pharmacokinetic study GS-02-517 (see 3.2.1), were allowed to be enrolled regardless of screening ALT or serum HBV DNA levels. All other entry criteria were to be met.

Patients with prior treatment with antiviral agents demonstrating anti-HBV activity within 6 months prior to the initial screening visit were not enrolled.

The CHMP noted that the inclusion criteria did not meet the definition of active, rapidly progressive CHB (persistently elevated plasma ALT levels > 3 ULN for ≥ 12 months). This population may not be representative of a population with active, progressive disease for which treatment should be considered in clinical practice.

Objectives

The primary objective was to investigate efficacy of ADV for the treatment of chronic hepatitis B (CHB) in children and adolescents (age 2 to < 18 years) compared to placebo following 48 weeks of treatment.

Initially the primary efficacy endpoint was the "proportion of subjects with serum HBV DNA<LLQ (lower limit of quantification) and ALT normalisation" and then changed to the proportion of subjects with serum HBV DNA < 1000 copies/ml and normal ALT at week 48. The LLQ of the HBV DNA assay was 29 IU/ml (equivalent to 169 copies/ml). This change favours the achievement of the endpoint and may not allow a direct comparison with study results in adults.

The CHMP had expressed the need to have a combined primary efficacy criterion to include HBe seroconversion (appearance of HBeAb) given the high rate of spontaneous seroconversion, (aprox 15% *per year*), in the paediatric population. The MAH considered that the inclusion of HBeAg seroconversion would significantly increased the sample size, and decided to keep seroconversion as a secondary criterion. A combined analysis of HbeAg seroconversion and HBV DNA < 1000 copies/ml and normal ALT at week 48 was however presented within the results.

The secondary objectives were:

• to investigate the safety of ADV for the treatment of CHB in children and adolescents (age 2 to < 18 years) compared to placebo at 48 weeks;

• to evaluate the proportion of children and adolescents who experience HBeAg and HBsAg seroconversion following 48 weeks;

• to evaluate the development of conserved site mutations associated with resistance to ADV;

• to evaluate the safety and efficacy of ADV in children and adolescents for up to 5 years.

Statistics

The analysis of the primary efficacy endpoint described in the Statistical Analysis Plan (finalised before unblinding the study) was a comparison of the treatment groups using 95% confidence intervals (CIs) of the difference between the groups (as well as between groups with data stratified by age group and by previous treatment for hepatitis B). However, another statistical method was chosen after unblinding the results. The MAH explained that due to the small number of responders in the placebo group, it was determined that a statistical exact test would be more appropriate in the evaluation of treatment group differences. The results analised by both methods and discussion on the relevant differences in the results if any, were not provided.

Results

Patients' disposition

A summary of the disposition of patients is present in the below table:

	2-6 years		7-11 years		12-17 years		Total	
	ADV (n=23)	Placebo (n=12)	ADV (n=36)	Placebo (n=19)	**ADV (n=56)**	**Placebo (n=27)**	**ADV (n=115)**	**Placebo (n=58)**
Randomised and treated	23	12	36	19	56	27	115	58
Completed 48 weeks	23 (100%)	12 (100%)	36 (100%)	19 (100%)	53 (95%)	27 (100%)	112 (97%)	58 (100%)
Discontinued prematurely:	0	0	0	0	3 (5%)	0	3 (3%)	0
▪ Adverse events	0	0	0	0	1 (2%)	0	1 (<1%)	0
▪ Non compliance	0	0	0	0	2 (4%)	0	2 (2%)	0

Demographic and baseline characteristics

There were no statistically significant differences between the ADV and placebo groups as regards demographic or baseline characteristics.

Subjects in the 7-11 years group and in the 12-17 years group had similar baseline characteristics: baseline median HBV DNA around 8.8 log10 copies/ml and median ALT levels around 2.3 ULN. Genotype A was the most common genotype in these age groups. The same proportion of subjects in each of these age groups were HBV therapy experienced-patients (aprox 70 %).

No data were available on the degree of necroinflammation in these children since a systematic biopsy was not required in the study.

In the targeted age group (12-17 years), ALT levels ranged from 0.7 to 10.4 ULN, showing that some children did not have any active disease at inclusion in the study and that an important variability in the severity of the disease was reported in this age group.

In addition, 3 subjects were HBeAg negative at baseline (1 in placebo 2-6 years, 2 in ADV 12-17 years) while the criterion for inclusion was HBeAg positivity. HBeAg negative patients tend to show a better treatment response than HBeAg positive as shown in previous studies.

It was noted that 9 subjects had normal ALT at baseline, although an inclusion criterion was ALT ≥ 1.5 × ULN. Four of these were in the 12-17 years old treatment group.

The small sample size of the patient population from 12 to 17 years in this study (56 ADV, 27 Placebo) and the heterogeneity of the disease status in this age group limited the study results interpretation.

Efficacy results

Serum HBV DNA < 1000 copies/ml and normal ALT

The primary efficacy endpoint results are summarised in the below table.

HBV DNA < 1000 copies/ml and Normal ALT	2-6 years		7-11 years		12-17 years		Total	
	ADV (n=23)	Placebo (n=12)	ADV (n=36)	Placebo (n=19)	ADV (n=56)	Placebo (n=27)	ADV (n=115)	Placebo (n=58)
Baseline (n, %)	0	0	0	0	0	0	0	0
Week 24 (n, %)	0	0	2 (6%)	0	4 (7%)	0	6 (5%)	0
End of blinded treatment (n,%)[a]	3 (13%)	1 (8%)	6 (17%)	0	13 (**23%**)	0	22 (19%)	1 (2%)
	p=1.00		p=0.083		p=0.007		p<0.001	

a Week 48 data, if week 48 result was missing, week 44 result was carried forward, if week 44 was missing, missing=failure

HBV DNA < 1000 copies/ml	2-6 years		7-11 years		12-17 years		Total	
	ADV (n=23)	Placebo (n=12)	ADV (n=36)	Placebo (n=19)	ADV (n=56)	Placebo (n=27)	ADV (n=115)	Placebo (n=58)
Baseline (n, %)	0	0	0	0	0	0	0	0
Week 24 (n, %)	0	0	5 (14%)	0	4 (7%)	0	9 (8%)	0
End of blinded treatment (n,%)[a]	4 (17%)	1 (8%)	7 (19%)	0	13 (23%)	0	24 (21%)	1 (2%)
	p=0.64		p=0.082		p=0.007		p<0.001	

Significantly more ADV-treated subjects in the 12−17 years age group achieved the primary efficacy endpoint (23% vs 0%, p = 0.007). The statistical significant difference between the ADV-treated and the placebo treated subjects (19% vs 2%; p<0.001) was mainly driven by the subjects in the group aged 12-17 years.

Although a statistically significant difference was noted, a more stringent criteria for the virological response (undetectability with at least a LLQ of ≤400 copies/ml) should have been used.

Change from baseline in serum HBV DNA

There was statistically significant difference between the ADV and placebo-treated subjects in each of the three age groups. However, for ADV-treated subjects, the magnitude of the change from baseline to week 48 decreased as the age of the subjects decreased:

- 12−17 year age group, median change was −3.46 log10 copies/ml (mean, −3.72);
- 7−11 year age group, median change was −3.27 copies/ml (mean, −3.38); and
- 2−6 year age group, median change was −2.78 copies/ml (mean, −3.19).

The median change in HBV DNA concentrations from baseline to week 48 were similar to those reported in adults (study -437) where a median change of -3.52 in ADV-treated patients *vs* -0.55 in placebo-treated patients was observed.

Categorical analysis of serum HBV DNA

Older subjects were more likely to have an HBV DNA < 1000 copies/ml than younger subjects, however it is noteworthy that with a more stringent criterion, a better response could be seen in younger children.

Only 4 patients (7%) with 12-17 years treated with ADV *vs* 0 treated with placebo had undetectable HBV DNA at week 48, whereas 13% *vs* 8% in the 2-6 years age group and 17% *vs* 0% in the 7-11 years age group achieved undetectability with ADV and placebo, respectively.

Furthermore, in the 12-17 years old group, a same proportion of patients achieved HBV DNA < 1000 copies/ml (23%) or had HBV DNA $>10^6$ copies/ml (27%). Overall, the response to adefovir therapy in the 12-17 years old was not convincing.

HBeAg seroconversion

There were no statistically significant differences between ADV−treated and placebo-treated HbeAg positive subjects in any of the three age groups (16% ADV *vs* 5% placebo, p = 0.051) as regards loss of HBeAg. However, when data from the 2−6 and 7−11 years groups (combined 2 to 11 age groups)

were pooled, there was a statistical difference between the treatment groups (20% ADV *vs* 0% placebo, p = 0.007).

A combined analysis of HBeAg seroconversion, decrease HBV DNA under 1000 copies/ml and ALT normalisation, was presented by the MAH:

HBeAg seroconversion, HBV DNA < 1000 copies/ml and Normal ALT	2-6 years		7-11 years		12-17 years		Total	
	ADV (n=23)	Placebo (n=12)	ADV (n=36)	Placebo (n=19)	ADV (n=56)	Placebo (n=27)	ADV (n=115)	Placebo (n=58)
Baseline (n, %)	0	0	0	0	0	0	0	0
Week 24 (n, %)	0	0	2 (6%)	0	2 (4%)	0	4 (4%)	0
End of blinded treatment (n,%)a	3 (13%)	0	5 (14%)	0	4 (7%)	0	12 (11%)	0
	p=0.54		p=0.15		p=0.30		p=0.009	

Only children treated with ADV achieved a response, however the difference between ADV and placebo groups was not statistically significant in any of the age groups. Only 4 (7%) ADV-treated patients aged 12-17 years had a positive response.

When the data were pooled for analysis, the difference between the treatment groups was statistically significant, when pooled for 2−11 years group (14% adefovir dipivoxil *vs* 0% placebo, p = 0.048) and when pooled for all three age groups (11% adefovir dipivoxil *vs* 0% placebo, p = 0.009).

Resistance

No subject developed the rtA181V or rtN236T mutation associated with ADV resistance over the 48 weeks. However, 5 ADV-treated patients (3 lamivudine-experienced and 2 naïve patients) developed mutations other than those *vs* none in placebo group. This did not translate into an identified impact on the virological response. Three lamivudine-experienced patients on ADV presented enrichment of the rtA181T mutation at week 48. Supplementary information provided by MAH showed that lamivudine was added to ADV treatment group causing a further decrease in HBV DNA but no further genotypic data was available.

The relationship between rtA181T mutation and phenotypic resistance to adefovir is under close monitoring for adult patients. It cannot be excluded that the development of rtA181T is a preliminary step of rtA181V emergence. The MAH has committed to provide the next annual resistance surveillance by the end of 2008 addressing any further genotypic change reported in this study.

Discussion and conclusion on efficacy

The 48 week efficacy data of this double-blind, randomised, placebo-controlled study showed that the proportion of HbeAg positive patients aged 12 to <18 years who achieved the primary efficacy endpoint (serum HBV DNA < 1000 copies/ml and normal ALT) was significantly higher in adefovir-treatment group in comparison with placebo treatment group, 23% (13/56) *vs* 0% (0/27). The HBV DNA levels change and the ALT levels change observed in this population are consistent with those reported in adult HbeAg positive patients (Hepsera pivotal study GS-02-437).

The CHMP had major concerns related to the methodological limitations of this paediatric pivotal study precluding the interpretation of the study results.

The small sample size with 56 ADV-treated patients and 27 placebo-treated in the targeted population of 12 to <18 year and the heterogeneity of baseline disease status and the level and identification of prior CHB treatment were limiting factors. Also the inclusion criteria did not meet the definition of active, rapidly progressive CHB (persistently elevated plasma ALT levels > 3 ULN for ≥ 12 months) as define currently in the European guidelines. Furthermore, for the targeted age group the baseline ALT levels ranged from 0.7 to 10.4 ULN showing that part of this small population did not have an active disease at inclusion and that there was an important variability in the severity of the disease in this age group.

Overall, this study population could not be considered as representative of a population with active, progressive disease for which treatment with adefovir should be considered in clinical practice.

As regards the study results, although a statistically significant difference was noted, a more stringent criteria for the virological response (undetectability with at least a LLQ of <400 copies/ml) should have been used. Also, given the high rate of spontaneous seroconversion, (aprox. 15% *per* year), in paediatric population, the primary efficacy criterion should have included HBe seroconversion (appearance of HBeAb).

Considering the methodological limitations of this pivotal paediatric study, including doubts on the baseline characteristics of the study population, the poorly convincing efficacy results observed in children aged 12 to <18 years old (in particular in term of HBeAg seroconversion) and considering the risk of emergence of resistance, the limited therapeutic options and the existence of cross resistance, the CHMP agreed that the clinical study did not provide confirmatory results to consider the use of adefovir more beneficial than deleterious in adolescents. The CHMP was of opinion that the clinical data available were insufficient to draw definitive conclusions.

These concerns were expressed to the MAH. However, as no further efficacy data that could provide reassurance on the therapeutic utility of ADV in paediatric patients was available, the MAH proposed not to pursue at this stage with an extension to the therapeutic indication for adefovir to include the treatment of adolescent patients.

The CHMP agreed to reflect the paediatric data in section 5.1 of the SPC. The information delivered in the SPC should however, be very limited and discourage off label use by highlighting the limitations of the efficacy demonstration in the overall paediatric population and not only in adolescent patients.

Clinical safety

An updated long term safety report was submitted as requested by the CHMP during the evaluation of this application. Available 96 week safety data included the ongoing open-label phase of the paediatric pivotal study GS-US-103-518 as well as additional information from the MAH drug safety and public health department database (DSPH).

Patient exposure

A total of 173 paediatric subjects with CHB were initially enrolled in the 48 week double blind phase of study -518 and received at least one dose of study treatment. The ongoing open-label phase includes a total of 162 paediatric subjects. The median exposure for the 12 – 17 years was 96 weeks.

Adverse events

Eighty four percent (84%) of the subjects in all ADV-groups experienced adverse events (AEs) over 48 weeks of treatment. A lower percentage of patients (72%) experienced AEs when data from 48 weeks plus open-label phase were combined.

The most frequently reported adverse events regardless of their relationship with the drug were nasopharynigitis (24%), headache (16%), pharyngitis (14%), cough (12%) and abdominal pain (12%). No difference with the double blind 48 week period was observed.

Between week 48 and week 96, new treatment-related adverse events reported in ADV–treated adolescents were: 1 hepatitis, 1 candidiasis, 1 blood CPK increased and 1 depression.
No additional cases of anorexia and/or decreased appetite attributed to ADV therapy was reported in adolescents in the second year of study.

Serious adverse events (SAEs) and deaths

No deaths were reported during the 96 week period of this study. In the 12-17 years age group, seven subjects (9%) had SAEs with ADV treatment from week 0 -96 (compared to 6% during the first 48 weeks). One patient reported depression and hepatitis which were the only drug-related SAEs.

Adverse events of special interest

- *Related to appetite*

A higher rate of anorexia, decreased appetite and/or decreased food intake in ADV treated patients compared to placebo treated patients (including some considered related to ADV) was seen at week 48.

Overall, at week 96, anorexia was reported in 4 subjects with adefovir dipivoxil treatment (5%) and decreased appetite was reported for 2 other subjects (3%) in the 12−17 year group with only one case occurred during the open label phase. None resulted in discontinuation of treatment. All were non-serious and two (one anorexia and one decreased of appetite) judged treatment related. One subject with decreased appetite also had an AE of decreased weight.

The performed analysis of vital signs (weight and height) showed a trend towards a lower weight gain from baseline to week 48 in ADV-treated paediatric patients (+2.5kg) compared to placebo-treated paediatric patients (+3.4kg). This trend was reported in each age group but more marked in younger children. Adjusted analysis by age group and prior hepatitis B treatment-experienced, the mean difference in change at week 48 was -1.2. No difference was however apparent in terms of change from baseline in height between both treatment groups.

An additional analysis of Body Mass Index (BMI) Z-scores will be submitted by Q1 2008 to further explore this issue.

- *Psychiatric disorders*

Six subjects (8%) in the 12−17 year group reported AEs in the "psychiatric disorders" system organ class during ADV treatment although mostly considered unrelated to study drug. Depression was the only drug-related SAEs in an adolescent with a history of depression. There is insufficient evidence at this stage to confirm that ADV therapy in adolescent plays a direct role in the occurrence of new-onset psychiatric disorders or aggravation of pre-existing conditions.
Psychiatric disorders are not listed in the Hepsera SPC. This issue will be closely monitored by the MAH.

- *Renal events*

No new safety concern was identified and no trend towards a higher susceptibility of paediatric population regarding the impact of ADV on renal function was identified in the 96 week safety data.

- *Hepatic events and on-treatment ALT flares*

No ADV−treated subject showed evidence of hepatic decompensation. In the 12-17 years group, during the double blind of ADV treatment no subject meet the definition of severe hepatic flare but in the open label treatment one had post-treatment exacerbation of hepatitis B. This subject had an SAE of Grade 3 hepatitis approximately 3 months after ADV treatment was discontinued due to depression.
Two subjects in this age group had marked abnormalities in ALT and/or in AST during ADV therapy.
No particular concern is raised by these findings that are in line with the known safety profile of ADV in adult patients.

- *Other laboratory abnormalities*

Serum Amylase and Lipase

Nine (5%) ADV treated subjects had treatment-emergent Grade 3 increases in serum amylase. Only one occurred in 12-17 year group and during the double blind period. Serum lipase concentrations were also concomitantly increased. There were no other relevant AEs at the same time.

Creatine phosphokinase (CPK)

In the 12−17 year group, CPK increase was the only marked laboratory abnormality during ADV treatment occurring in six subjects (8%). All CPK elevations resolved during ongoing ADV treatment.

Discontinuation due to AEs

Two ADV treated subjects permanently discontinued study treatment because of an AE. Both subjects were in the 12−17 year group (one reported in the 48 week). Both had pre-existing psychiatric disorders. In one case the patient developed a worsening of his abnormal behaviour, and the other experienced treatment-related depression. The role of ADV is unclear. An aggravation of pre-existing symptoms cannot however be excluded.

Additional safety information
Fifteen additional reports of SAEs in paediatric subjects were identified on the MAH database, in subjects who are or were enrolled in GS-US-103-518. These events were not yet in the clinical study database at the time of the data cut-off for this update.
Ten were hepatic SAEs, nine of which occurred after discontinuation of ADV treatment because of either seroconversion or an inadequate response to treatment. Five of them occurred in the 12-17 age group.

Discussion and conclusion on safety
Overall, the 96-week safety data reported in study GS-US-103-0518 confirmed that the safety profile of adefovir in adolescent is comparable to the known safety profile in adult population.

No major concern was raised, in particular renal events and hepatic decompensation. Most of the adverse reactions related to adefovir treatment are already listed in the Hepsera SPC for adult patients.

Higher rates of anorexia, decreased appetite and/or decreased food intake, currently unlisted, were reported in adefovir treated patient compared to placebo, during the double blind phase of this study. No additional cases were reported in adolescent in the second year of study.
The analysis on BMI scores to be submitted by Q1 2008 are expected to address the remaining concern with regard to the lower weight change from baseline to week 48 observed in the adefovir group (-1.2kg). The 96 weeks data on vital signs (body weight, height and BMI) will also be provided.

Seven cases of psychiatric disorders were reported. Since an aggravation of pre-existing conditions due to adefovir therapy cannot be excluded, the CHMP recommended that this issue should be monitored.

Overall conclusion and Benefit-Risk assessment
CHB infection in children, including adolescents, is characterised by a more benign disease and a relatively high annual rate of spontaneous and durable seroconversion as compared to adults. There is a particular need to be convinced on the benefit of the treatment and to have reassurance on its safety profile before any recommendation on its use in the paediatric population could be granted.

In view of the methodological limitations of the pivotal paediatric study, including uncertainty of the active, progressive disease of the study population, the poorly convincing efficacy results observed in children aged 12 to <18 years old (in particular in term of HBeAg seroconversion) and the uncertainties surrounding the long-term safety profile of this drug in children, the CHMP was of opinion that the efficacy and safety data available do not allow to make a benefit/risk assessment of adefovir in this specific population.

Given the risk of emergence of resistance, the limited therapeutic options and the existence of cross resistance, an early introduction (longer treatment duration) of antiviral treatment in children, this clinical study does not provide convincing arguments to consider that the use of adefovir might be more beneficial than deleterious in adolescents.

The MAH, acknowledging the CHMP concerns, proposed not to pursue an extension of indication for Hepsera in adolescent patients at this stage.

It was also agreed that the clinical development of adefovir in children should be reflected in the SPC.

Conclusion
On 24 January 2008 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics.