EUROPEAN MEDICINES AGENCY
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Committee for Medicinal Products for Human Use (CHMP)

# Hepsera

(adefovir dipivoxil)

Procedure No. EMEA/H/C/000485/P46/066

# CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006



**Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted**

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# Rapporteur's Assessment Report for Post-Authorisation Commitments (PACs)

**for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended P46 - Paediatric Article 46**

**+**

**FU2 028.7 (clinical FUM9)**

***long-term durability of HBeAg or HBsAg seroconversions***

# Hepsera
# (adefovir dipivoxil)

# EMEA/H/C/000485

# Marketing Authorisation Holder: Gilead Sciences International Ltd.



| | |
|---|---|
| **Rapporteur:** | P. Lechat |
| **Date of this report:** | 29.08.2011 |
| **Deadline for CHMP member's comments:** | 05.09.2011 |
| **Date of the Final report:** | |

# I. INTRODUCTION

Gilead submitted the **final clinical report for Study GS-US-103-0518** *A Phase 3 Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of Adefovir Dipivoxil in Children and Adolescents (Age 2 to < 18) with Chronic Hepatitis B* **in accordance with Article 46 of Regulation** (EC) No 1901/2006.
A short critical expert overview has also been provided.

Gilead stated that study GS-US-103-0518 is a stand alone study and in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for adefovir dipivoxil and therefore do not require taking further regulatory action on the marketing authorisation for Hepsera.

In addition, in accordance with **FU2 028** (FUM 9), additional analyses of the presence of basal core promoter and pre-core mutations at baseline among hepatitis B e antigen (HBeAg) positive paediatric patients were conducted in Study GS-US-103-0518. These results are still being gathered. However, preliminary data has been provided and are discussed in the current report.



# II. SCIENTIFIC DISCUSSION

## II.1 Information on the development program

The pediatric development program for ADV included 4 studies: 3 completed clinical pharmacology studies (GS-02-515, GS-02-517, and GS-02-536 final Clinical Study Reports were submitted **in June 2007** with the Type II variation to extend the pediatric indication **to include treatment of adolescent patients, Hepsera type II variation II30**) and a recently completed pediatric efficacy and safety study (GS-US-103-0518).

Study **GS-US-103-0518** was designed to evaluate the efficacy and safety of ADV in pediatric subjects with CHB who were 2 to < 18 years old at the time of the first dose of study treatment. Forty-eight weeks interim efficacy and safety data were provided from this study as part of the Type II variation II30. The ADV doses were based on the findings of a Phase 1/2 clinical pharmacology study conducted in 45 pediatric subjects with CHB (Study GS-02-517). An investigational ADV oral suspension was used in subjects 2–11 years old and the marketed 10-mg ADV tablet was used in subjects 12 to17 years old. The investigational oral suspension formulation was developed to allow age- and weight-based dosing of pediatric patients for the purpose of evaluating the efficacy and safety of the drug in pediatric patients. The effects of long-term therapy with ADV in this patient population were to be assessed in this 5-year study.

On the basis of the Week 48 data from Study GS-US-103-0518, Hepsera tablets was approved for the treatment of adolescents (≥ 12 years of age) with CHB by the US Food and Drug Administration on 19 December 2007.

*Rapporteur's comment: In Europe, the CHMP concluded that the 48 weeks data from the pivotal paediatric study GS-US-103-0518 did not provide convincing arguments to consider that the use of adefovir might be more beneficial than deleterious in adolescents. Methodological limitations, poorly convincing efficacy results (notably for HBeAg seroconversion) and uncertainties as regards the long-term safety profile of the drug in children were pointed out. As a consequence, the MAH, acknowledging the CHMP concerns, proposed not to pursue an extension of indication for Hespera in adolescent patients at this stage.*

**The current submission presents the results of the open-label portion of the study (Weeks 49 to 240).**

## II.2 Clinical aspects (open-label period from study GS-US-103-0518)

### A. EFFICACY

- *study design*

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| ***Title*** | A Phase 3 Double-Blind, Randomized, Placebo- Controlled Study of the Safety and Efficacy of Adefovir Dipivoxil in Children and Adolescents (Age 2 to < 18) with Chronic Hepatitis B. |
| **Study centers** | 26 study centers: United States (12 centers), Poland (5), Germany (4), United Kingdom (3), Belgium (1), and Spain (1) |
| **Study start Date**<br>**Data cut-off Date** | 17 May 2004 (First subject screened)<br>09 April 2010 (Last subject observation) |
| **Objectives/ Endpoints** | **Primary objective:**<br>• To investigate the efficacy of adefovir dipivoxil (ADV) for the treatment of CHB in children and adolescents (age 2 to < 18) compared to placebo following 48 weeks of treatment.<br>The primary endpoint was the proportion of subjects with serum **HBV DNA < 1000 copies/mL and normal ALT** at Week 48<br><br>**Secondary objectives:**<br>• To investigate the safety of ADV for the treatment of CHB in children and adolescents (age 2 to < 18) compared to placebo following 48 weeks of treatment.<br>• To evaluate the proportion of children and adolescents who experience HBeAg and HBsAg seroconversion following 48 weeks of treatment with ADV or placebo.<br>• To evaluate the development of conserved site mutations associated with resistance to ADV.<br>• To evaluate the safety (including assessment of growth and renal function) and efficacy of ADV in children and adolescents for up to 5 years. |
| **Methodology** | **There were two study periods:**<br><u>Weeks 0−48 (Study Year 1):</u><br>The first 48 weeks of the study were a randomized, **double-blind, placebo-controlled,** parallel-group treatment period. Subjects were randomly assigned to treatment in a **2:1** fashion to ADV or placebo. Prior to randomization, eligible subjects were classified into one of 6 **strata** based upon **age** at screening (2 to < 7 years; ≥ 7 to < 12 years; ≥ 12 to < 18 years) and **prior exposure to treatment** for CHB (prior treatment; no prior treatment).<br><br>**<u>Weeks 49−240 (Study Years 2−5):</u>**<br>**At Week 48, all placebo-treated subjects who did not exhibit HBeAg or HBsAg seroconversion at Week 44, plus all ADV−treated subjects, were offered the opportunity to receive open-label ADV for up to an additional 192 weeks.** Any subject with **HBV DNA ≥ 1000 copies/mL at 2 consecutive visits 12 weeks apart was to be discontinued from open-label study treatment.** The only exception was for subjects in the adolescent age range with prior lamivudine experience who were allowed the opportunity to add lamivudine to ADV; similarly if combination failed to impart suppression of HBV DNA below 1000 copies/mL (confirmed) discontinuation was necessary.<br>All subjects who discontinued study drug due to confirmed seroconversion were requested to continue to return for study visits for the remainder of the study in order to evaluate the durability of seroconversion. Subjects who wished to discontinue study treatment and withdraw from the study prior to study completion were requested to return every 4 weeks for 16 weeks for posttreatment evaluations following an early termination visit. Any subjects who experienced posttreatment hepatic flares during the 16-week followup period were to be followed every 4 weeks until their alanine aminotransferase (ALT) levels returned to ≤ 2 × the upper limit of normal (ULN) for a maximum off-treatment follow-up of 6 months. Subjects who experienced a severe hepatic flare (per protocol definition) after discontinuation of ADV |

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| | during the open-label treatment period may have been eligible to receive ADV provided by Gilead, after consultation with the Gilead medical monitor, for treatment of the hepatic flare. |
| **Population** | The study enrolled **treatment-naive and treatment-experienced** pediatric subjects (2 to < 18 years old at the first dose of study treatment) who had **HBeAg+** CHB, were HBsAg+ for ≥ 6 months prior to randomization and at screening, had serum hepatitis B virus (HBV) DNA ≥ $10^5$ copies/mL, **compensated** liver disease, and calculated creatinine clearance ≥ 80 mL/min. |
| **Number of subjects** | **Planned for 48-week** Randomized Period: ≥ 150 subjects<br>**Analyzed for 48-week** Randomized Period: 173 subjects<br>**Analyzed for 240-week** Open-Label Period: 162 subjects |

| Analysis Set | ADV-ADV | PLB-ADV | Total |
|---|---|---|---|
| Full Analysis Set | 115 | 58 | 173 |
| Open-Label Analysis Set | 108 | 54 | 162 |

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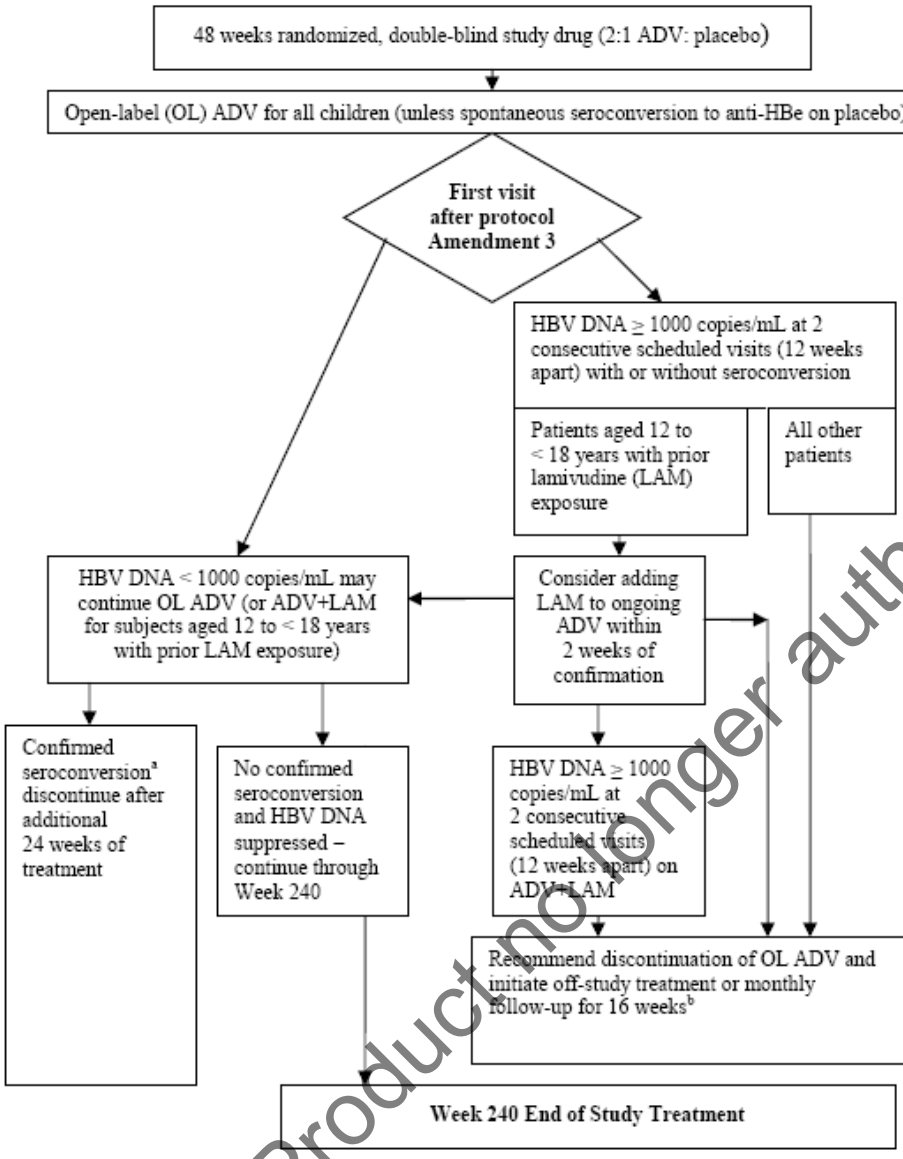
|---|---|
| **Duration of Treatment:** | **Forty-eight weeks** of treatment with ADV or placebo. After 48 weeks of treatment, eligible subjects had the opportunity to continue treatment with open-label ADV from **Weeks 49−240**.<br><br>**Treatment with ADV:**<br>• Subjects 2 to < 7 years: investigational oral suspension of ADV, 0.3 mg/kg once daily<br>• Subjects ≥ 7 to < 12 years: investigational oral suspension of ADV, 0.25 mg/kg once daily<br>• Subjects ≥ 12 to < 18 years: ADV tablet (marketed formulation), 10 mg once daily<br>The ADV dose was not to exceed 10 mg/day. |

## GS-US-103-0518: Flow Diagram for Weeks 49–240(Amendment 3)




a Children with confirmed seroconversion to anti-HBe (or anti-HBs) on OL ADV (2 consecutive visits at least 12 weeks apart) and HBV DNA < 1000 copies/mL had OL ADV discontinued at the next scheduled visit (approximately 24 weeks post seroconversion) and were followed monthly off drug for 16 weeks and then per the routine, protocol-specified visit schedule.

b On a case-by-case basis, an investigator may have determined that the benefit of continuing ADV, despite suboptimal suppression of HBV, clearly outweighed the risk of resistance development. In such instances Gilead continued to provide ADV for up to 24 weeks and regular monitoring of the subject's HBV DNA and resistance surveillance as per the protocol.



*<u>Rapporteur's comment:</u> As illustrated above, during the open-label phase of the study patients could be withdrawn from adefovir if either :*
*- they had respond to therapy, i.e. had HBV DNA<1000 copies/ml and achieved HBeAg seroconversion; or if, on the contrary:*
*- they failed to suppress HBV DNA, i.e. they had HBV DNA> 1000 copies/ml under ADV (or under ADV+LAM in treatment-experienced adolescents patients)*
*As a consequence, patients who remained on ADV during the open-label phase of the study were patients who achieved HBV DNA < 1000 copies/ml and tolerated study drug. However, on a case-by-case basis, regardless of age or prior lamivudine exposure, an investigator may have determined that the benefit of continuing ADV, despite suboptimal suppression of HBV, clearly outweighed the risk of resistance development.*
*Overall, a heterogenous population of patients were on study drug or off drug during the open-label study. Some difficulties in the interpretation of results for the open-label phase might be anticipated.*

- *characteristics of the study population*

A total of 173 subjects were randomized and treated (115 ADV, 58 placebo). 170 completed the 48-week study, of which **162 participated in the open-label period of the study.**

**GS-US-103-0518: Subject Disposition during the Open-Label Period - All Age Groups (Open-Label Analysis Set)**

| Subject Disposition | OL ADV (DB ADV) | OL ADV (DB PLB) | Overall |
|---|---|---|---|
| Randomized | 108 | 54 | 162 |
| Received Open-Label ADV | 108 | 54 | 162 |
| Received Lamivudine after Week 48 | 12 (11.1%) | 10 (18.5%) | 22 (13.6%) |
| Discontinued Study Drug During Year 2 | 13 (12.0%) | 2 (3.7%) | 15 (9.3%) |
| Reason: HBeAg or HBsAg seroconversion | 9 (69.2%) | 2 (100.0%) | 11 (73.3%) |
| Adverse Event/Intercurrent Illness | 1 (7.7%) | 0 | 1 (6.7%) |
| Missing | 1 (7.7%) | 0 | 1 (6.7%) |
| Subject noncompliance | 1 (7.7%) | 0 | 1 (6.7%) |
| Subject withdrew consent | 1 (7.7%) | 0 | 1 (6.7%) |
| Discontinued Study During Year 2 | 2 (1.9%) | 0 | 2 (1.2%) |
| Reason: Adverse Event/Intercurrent Illness | 1 (50.0%) | 0 | 1 (50.0%) |
| Subject withdrew consent | 1 (50.0%) | 0 | 1 (50.0%) |
| Completed the 96-week Study Treatment Period | 106 (98.1%) | 54 (100.0%) | 160 (98.8%) |
| Discontinued Study Drug During Year 3 | 51 (47.2%) | 21 (38.9%) | 72 (44.4%) |
| Reason: Other | 29 (56.9%) | 10 (47.6%) | 39 (54.2%) |
| HBeAg or HBsAg seroconversion | 18 (35.3%) | 9 (42.9%) | 27 (37.5%) |
| Missing | 1 (2.0%) | 1 (4.8%) | 2 (2.8%) |
| Subject noncompliance | 1 (2.0%) | 1 (4.8%) | 2 (2.8%) |
| Lost to follow-up | 1 (2.0%) | 0 | 1 (1.4%) |
| Subject withdrew consent | 1 (2.0%) | 0 | 1 (1.4%) |
| Discontinued Study During Year 3 | 25 (23.1%) | 9 (16.7%) | 34 (21.0%) |
| Reason: Other | 22 (88.0%) | 8 (88.9%) | 30 (88.2%) |
| Subject withdrew consent | 2 (8.0%) | 0 | 2 (5.9%) |
| Lost to follow-up | 1 (4.0%) | 0 | 1 (2.9%) |
| Subject noncompliance | 0 | 1 (11.1%) | 1 (2.9%) |
| Completed the 144-week Study Treatment Period | 81 (75.0%) | 45 (83.3%) | 126 (77.8%) |
| Discontinued Study Drug During Year 4 | 25 (23.1%) | 13 (24.1%) | 38 (23.5%) |
| Reason: Other | 13 (52.0%) | 7 (53.8%) | 20 (52.6%) |
| HBeAg or HBsAg seroconversion | 7 (28.0%) | 3 (23.1%) | 10 (26.3%) |
| Missing | 2 (8.0%) | 2 (15.4%) | 4 (10.5%) |
| Progression of disease | 1 (4.0%) | 1 (7.7%) | 2 (5.3%) |
| Subject noncompliance | 2 (8.0%) | 0 | 2 (5.3%) |

| Subject Disposition | OL ADV (DB ADV) | OL ADV (DB PLB) | Overall |
|---|---|---|---|
| Discontinued Study During Year 4 | 21 (19.4%) | 9 (16.7%) | 30 (18.5%) |
| Reason: Other | 15 (71.4%) | 8 (88.9%) | 23 (76.7%) |
| Subject noncompliance | 4 (19.0%) | 0 | 4 (13.3%) |
| Progression of disease | 2 (9.5%) | 1 (11.1%) | 3 (10.0%) |
| Completed the 192-week study treatment period | 60 (55.6%) | 36 (66.7%) | 96 (59.3%) |
| Discontinued Study Drug During Year 5 | 7 (6.5%) | 4 (7.4%) | 11 (6.8%) |
| Reason: HBeAg or HBsAg seroconversion | 4 (57.1%) | 3 (75.0%) | 7 (63.6%) |
| Other | 1 (14.3%) | 1 (25.0%) | 2 (18.2%) |
| Missing | 1 (14.3%) | 0 | 1 (9.1%) |
| Did not respond to study drugs | 1 (14.3%) | 0 | 1 (9.1%) |
| Discontinued Study During Year 5 | 14 (13.0%) | 1 (1.9%) | 15 (9.3%) |
| Reason: Other | 10 (71.4%) | 0 | 10 (66.7%) |
| Subject withdrew consent | 3 (21.4%) | 0 | 3 (20.0%) |
| Lost to follow-up | 0 | 1 (100.0%) | 1 (6.7%) |
| Subject noncompliance | 1 (7.1%) | 0 | 1 (6.7%) |
| Completed the 240-week Study Period (either on or off drug at Week 240) | 46 (42.6%) | 35 (64.8%) | 81 (50.0%) |
| Completed the 240-week Study Treatment Period (on drug at Week 240) | 12 (11.1%) | 14 (25.9%) | 26 (16.0%) |
| Completed 240-week Study Treatment and Receiving Lamivudine (either on or off drug at Week 240) | 9 (19.6%) | 8 (22.9%) | 17 (21.0%) |
| Completed the 240-week Study Period (either on or off drug at Week 240) and Entered Treatment-free Follow-up | 43 (39.8%) | 28 (51.9%) | 71 (43.8%) |
| Completed the 240-week Study Treatment Period (on drug at Week 240) and Entered Treatment-free Follow-up | 9 (8.3%) | 7 (13.0%) | 16 (9.9%) |

OL = open-label, ADV = adefovir dipivoxil, PLB = placebo

The OL analysis set includes any subject that took at least one dose of OL ADV.

Programming Details: Year5_analysis\Version_1\intext\n_tab2rtf.sas v9.1 Output file: t_disp1.out 16JUN2010:17:21



Of the 162 subjects who participated in the open-label period, 81 subjects (46 ADV-ADV, 35 PLB-ADV) completed the open-label study period, and 71 of these subjects (43 ADV-ADV, 28 PLB-ADV) entered treatment-free follow-up. A total of 26 subjects completed Week 240 on study drug (12 ADV-ADV, 14 PLB-ADV). Of these 26 subjects, 17 were on a combination of lamivudine plus ADV per virologic failure criteria stipulated in Amendment 3.

**A total of 136 subjects (96 ADV-ADV, 40 PLB-ADV) discontinued study drug between Weeks 48 and 240.** The reasons for study drug discontinuation were **HBsAg or HBeAg seroconversion (55 subjects), other (61 subjects),** missing (8 subjects), subject noncompliance (5 subjects), withdrew consent (2 subjects), progression of disease (2 subjects), adverse event/intercurrent illness (1 subject), lost to follow-up (1 subject), and nonresponse to study drugs (1 subject).).

In the 12 to 17 year-old age group, of the 75 subjects, 57 subjects (42 ADV-ADV; 15 PLB-ADV) discontinued the study drug between Weeks 48 and 240. The most common reasons for discontinuing the study drug were other (25 subjects), HBeAg or HBsAg seroconversion (22 subjects).

*Rapporteur's comment: Only half of the patients (n=81/162) completed the 5-year study period (either on or off drug at week 240) and among them 71 patients entered treatment-free follow-up, which makes the assessment of the long term data rather limited.*

*Among the 162 patients who entered open-label period, 26 (16%) were still on ADV at the end of the 5 year study; 55 patients (34%) discontinued study drug following "success" (HBe- or HBs- Ag seroconversion); most (56%) of the patients discontinued study drug for "other reasons" (many due to treatment failure).*

Demographics and baseline characteristics data for the open-label period (n = 162) were similar between the ADV-ADV and PLB-ADV groups. The mean age (11 years) and age range (2 to 17) were the same in both groups. Males comprised 63.0% of the ADV-ADV subset, and comprised 68.5% of the group assigned to PLB-ADV. Racial distribution was similar across both groups, with 61.1% White and 26.9% Asian in the ADV-ADV group and 72.2% White and 18.5% Asian in the PLB-ADV group.
The majority of subjects had HBV genotype A at baseline (48.8%). Most (57%) were treatment-experienced patients. Mean (SD) baseline HBV DNA was 8.8 (0.82) log10 copies/mL and median ALT levels were 2.3 ULN; which was similar between the 2 treatment groups.

*<u>Rapporteur's comment:</u> Baseline characteristics of the open-label analysis set were similar to the baseline characteristics of the global study population, i.e. not a population with active CHB.*

- *Results*

*As a reminder, primary efficacy endpoint (HBV DNA < 1000 copies/mL plus Normal ALT) results from the study Week 48 analysis were the following:*

| HBV DNA < 1000 copies/mL and Normal ALT (n, %) | 2–6 Years [a] | | 7–11 Years [a] | | 12–17 Years [a] | | Total | |
|---|---|---|---|---|---|---|---|---|
| | ADV (n=23) | PLB (n=12) | ADV (n=36) | PLB (n=19) | ADV (n=56) | PLB (n=27) | ADV (n=115) | PLB (n=58) |
| **Baseline** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** |
| **End of Blinded Treatment [b]** | **3 (13%)** | **1 (8%)** | **6 (17%)** | **0** | **13 (23%)** | **0** | **22 (19%)** | **1 (2%)** |
| **p-value [c]** | **p = 1.00** | | **p = 0.083** | | **p = 0.007** | | **p < 0.001** | |

Randomized-and-Treated (RAT) analysis set
ADV = adefovir dipivoxil, PLB = placebo
a Age at first dose of study treatment; ranges are inclusive (ie, 2 to < 7 years; ≥ 7 to < 12 years; ≥ 12 to < 18 years)
b Week-48 data; if Week 48 was missing, Week 44 was carried forward; if Week-44 was missing, missing = failure
c Fisher's Exact test (ADV versus placebo at end of blinded treatment); missing = failure analysis

*Of note, in view of the poor results in the 2-6 and 7-11 years children included in study GS-US-103-0518, the Applicant did not apply for an extension of the indication in these age groups and only requested to extend the indication of Hepsera to adolescents.*

*<u>Summary of CHMP conclusion on the 48 weeks efficacy data</u> (made in the setting of VAR II30 in 2008):*
*"The proportion of children aged 12 to <18 years old who achieved the primary endpoint (serum HBV DNA < 1000 copies/ml and normal ALT at 48 weeks) was significantly higher in adefovir-treated patients when compared to placebo-treated patients (ADV: 12 (23%) vs Placebo: 0).*
*However, before encouraging the use of adefovir of adolescents by granting an indication in this target population, several issues need to be carefully weighted.*
*- **the study population has particular limitations** :*
- *limited sample size : ADV: n=56, Placebo: n=27*
- *does not strictly match the population targeted in clinical practice with active, progressive disease*

*In this study patients were eligible if they had ALT levels ≥ 1.5 ULN. Therefore, a significant part of*

*the small population included in this pivotal study have minimal hepatitis disease.*

- *the **definition of the primary endpoint is not optimal** since it does not include the rate of HBeAg seroconversion.*
- *As a matter of fact, the significant **antiviral efficacy of adefovir is no longer apparent** on the **relevant endpoint combining serum HBV DNA < 1000 copies/ml, normal ALT and HBeAg seroconversion** (there is no statistically significant difference on the proportion of patients who achieved this combined endpoint : ADV 7%, placebo 0%).*

*These results are explained by the fact that **no difference was observed over the placebo arm in term of HBeAg seroconversion in children above 12 years old (11% vs 11%).***

- *Given the low LLQ of the HBV DNA assay used in this study (i.e. 169 copies/ml), **a more stringent criterion of the virological response might have been chosen** for the primary endpoint.*

*Surprisingly, with the stringent definition of decrease of HBV DNA to undetectable level (at 169 copies/ml), a better response is observed in younger children when compared to adolescents (whereas they were considered as poorer responders on the proportion of patients achieving HBV DNA < 1000 copies/ml). Indeed, only 4 patients (7%) achieved undetectability in the 12-17 years age group (versus 13% and 17% in the age groups 2-6 and 7-11, respectively)."*

*A major objection was raised by the CHMP. The MAH acknowledging the CHMP concern decided not to pursue an extension of HESPERA in adolescents.*

**- ADV Open-label Period (current submission):**

**The key Secondary Efficacy Endpoints from open-label period of study GS-US-103-0518 are presented below:**

*Mean change from baseline in HBV DNA level*

The decreasing trend in mean serum HBV DNA continued over time after ADV Week 48 in both treatment groups, at which time mean change was −3.43 log10 copies/mL (standard deviation [SD] 1.561) in the ADV-ADV on-treatment group (n=106) and −3.69 log10 copies/mL (SD 1.658) in the PLB-ADV on-treatment group (n=50).

By ADV Week 240, mean change from ADV baseline in HBV DNA was −5.87 log10 copies/mL (SD 1.826) in the ADV-ADV on-treatment group (n=7) and only slightly smaller in the ADV-ADV off-treatment group (n=39) at Week 240 (−5.02 log10 copies/mL, SD 1.474).

At ADV Week 192 (last ADV time point for the PLB-ADV group), mean change from ADV baseline in HBV DNA for the PLB-ADV on-treatment group (n=9) was −5.41 log10 copies/mL (SD 1.573). For those in the PLB-ADV off-treatment group at Week 192 (n=26), mean change was smaller (−4.46 log10 copies/mL, SD 1.701).

**GS-US-103-0518: Summary of Key Efficacy Endpoints through Last ADV Time Point, All Age Groups, Open-Label Analysis Set**

| ADV Time Point[a] | On-Trt OL ADV (DB ADV) | On-Trt OL ADV (DB PLB) | On-Trt OL Overall | Off-Trt OL ADV (DB ADV) | Off-Trt OL ADV (DB PLB) | Off-Trt OL Overall |
|---|---|---|---|---|---|---|
| **HBV DNA < 1000 copies/mL (M=F)** | | | | | | |
| Baseline | 0/108 (0.0%) | 0/54 (0.0%) | 0/162 (0.0%) | 0/108 (0.0%) | 0/54 (0.0%) | 0/162 (0.0%) |
| Week 48 | 19/108 (17.6%) | 12/54 (22.2%) | 31/162 (19.1%) | 0/108 (0.0%) | 0/54 (0.0%) | 0/162 (0.0%) |
| Week 96 | 22/108 (20.4%) | 18/54 (33.3%) | 40/162 (24.7%) | 7/108 (6.5%) | 3/54 (5.6%) | 10/162 (6.2%) |
| Week 144 | 13/108 (12.0%) | 17/54 (31.5%) | 30/162 (18.5%) | 12/108 (11.1%) | 4/54 (7.4%) | 16/162 (9.9%) |
| Week 192 | 16/108 (14.8%) | 8/54 (14.8%) | 24/162 (14.8%) | 11/108 (10.2%) | 11/54 (20.4%) | 22/162 (13.6%) |
| Week 240 | 6/108 (5.6%) | 0 | 6/108 (5.6%) | 16/108 (14.8%) | 0 | 16/108 (14.8%) |
| **HBV DNA < 1000 copies/mL at Last On-treatment Visit** | | | | | | |
| Last On-treatment Visit | 46/108 (42.6%) | 33/54 (61.1%) | 79/162 (48.8%) | NA | NA | NA |
| **ALT Normal (M=F)** | | | | | | |
| Week 48 | 64/108 (59.3%) | 33/54 (61.1%) | 97/162 (59.9%) | 0/108 (0.0%) | 3/54 (5.6%) | 3/162 (1.9%) |
| Week 96 | 61/108 (56.5%) | 21/54 (38.9%) | 82/162 (50.6%) | 13/108 (12.0%) | 12/54 (22.2%) | 25/162 (15.4%) |
| Week 144 | 28/108 (25.9%) | 17/54 (31.5%) | 45/162 (27.8%) | 28/108 (25.9%) | 15/54 (27.8%) | 43/162 (26.5%) |
| Week 192 | 15/108 (13.9%) | 7/54 (13.0%) | 22/162 (13.6%) | 26/108 (24.1%) | 23/54 (42.6%) | 49/162 (30.2%) |
| Week 240 | 5/108 (4.6%) | 0 | 5/108 (4.6%) | 37/108 (34.3%) | 0 | 37/108 (34.3%) |
| **HBeAg Loss (M=E)[b]** | | | | | | |
| Week 48 | 14/103 (13.6%) | 11/48 (22.9%) | 25/151 (16.6%) | 0 | 2/3 (66.7%) | 2/3 (66.7%) |
| Week 96 | 20/84 (23.8%) | 5/28 (17.9%) | 25/112 (22.3%) | 15/19 (78.9%) | 11/14 (78.6%) | 26/33 (78.8%) |
| Week 144 | 11/33 (33.3%) | 4/18 (22.2%) | 15/51 (29.4%) | 29/38 (76.3%) | 16/16 (100.0%) | 45/54 (83.3%) |
| Week 192 | 9/16 (56.3%) | 3/9 (33.3%) | 12/25 (48.0%) | 29/39 (74.4%) | 18/22 (81.8%) | 47/61 (77.0%) |
| Week 240 | 2/6 (33.3%) | 0 | 2/6 (33.3%) | 36/39 (92.3%) | 0 | 36/39 (92.3%) |
| **HBeAg Seroconversion (M=E)[b, c]** | | | | | | |
| Week 48 | 13/103 (12.6%) | 11/48 (22.9%) | 24/151 (15.9%) | 0 | 2/3 (66.7%) | 2/3 (66.7%) |
| Week 96 | 17/83 (20.5%) | 4/28 (14.3%) | 21/111 (18.9%) | 15/19 (78.9%) | 11/14 (78.6%) | 26/33 (78.8%) |
| Week 144 | 9/33 (27.3%) | 3/18 (16.7%) | 12/51 (23.5%) | 29/38 (76.3%) | 14/15 (93.3%) | 43/53 (81.1%) |
| Week 192 | 7/16 (43.8%) | 1/9 (11.1%) | 8/25 (32.0%) | 28/39 (71.8%) | 18/22 (81.8%) | 46/61 (75.4%) |
| Week 240 | 1/6 (16.7%) | 0 | 1/6 (16.7%) | 35/39 (89.7%) | 0 | 35/39 (89.7%) |
| At Last On- or Off-treatment Visit | 46/107 (43.0%) | 22/53 (41.5%) | 68/160 (42.5%) | 50/ 96 (52.1%) | 23/39 (59.0%) | 73/135 (54.1%) |

ADV = adefovir dipivoxil, DB = double blind, M=E = missing equals excluded, M=F = missing equals failure, NA = not applicable, OL = open label, PLB = placebo, Trt = treatment

a ADV baseline= the day of first dose of ADV; ADV Week = the windowed visit week relative to ADV baseline.

b Analysis set consisted of open-label analysis set subjects who were HBeAg+ at ADV baseline.

c HBeAg seroconversion is defined as HBeAg negative and anti-HBe positive or borderline, for subjects with HBeAg positive at study baseline.

*HBV DNA<1000 copies/ml*
After Week 72, the percentage of subjects in the ADV-ADV on-treatment group with HBV DNA below 1000 copies/mL declined overall, dropping to 5.6% (6/108 subjects) by ADV Week 240, based on an analysis in which subjects with missing data were considered as failures (Missing=Failure analysis). After ADV Week 48, the percentage of subjects in the PLB-ADV on-treatment group with HBV DNA below 1000 copies/mL increased to 33.3% (18/54 subjects) at ADV Week 96, and decreased to 14.8% (8/54 subjects) by ADV Week 192. For the ADV-ADV on-treatment group at Week 192, 14.8% (16/108 subjects) had HBV DNA below 1000 copies/mL.
When considering only the patients who remained on ADV (as reflected by Missing=Excluded analysis), the percentage in the ADV-ADV on-treatment group with HBV DNA below 1000 copies/mL at ADV Week 192 was 94.1% (16/17 subjects), and was somewhat lower by ADV Week 240 (6/7 subjects, 85.7%). The percentage of subjects in the PLB-ADV on-treatment group with HBV DNA below 1000 copies/mL was 100% at ADV Week 132 (18/18 subjects), and was 88.9% (8/9 subjects) by ADV Week 192.

Due to the number of discontinuations in this study (of importance, discontinuation was required per protocol if HBV DNA was confirmed ≥ 1000 copies/mL), the last on-treatment HBV DNA results are relevant. Overall about half of the subjects had HBV DNA below 1000 copies/mL at the last on-treatment visit. In the ADV-ADV group 42.6% (46/108 subjects) had HBV DNA values below 1000 copies/mL, and in the PLB-ADV group 61.1% (33/54 subjects) were below this threshold at the last on-treatment visit.

*Normal ALT*
The percentage of subjects of any age with normal ALT for both the on-treatment ADV-ADV and PLB-ADV groups generally decreased over time after ADV Week 48, while the opposite was true for those in both off-treatment groups (M=F analysis).

*Age group 12 to 17 years*
Of note, there were no notable differences in HBV DNA and ALT endpoints based on subgroup analyses of subjects aged 12 to 17 years versus those based on all age groups combined.

*HBe seroconversion*
Overall, 68/160 subjects (42.5%) on treatment at their last visit had experienced HBeAg seroconversion, and 73/135 subjects (54.1%) off treatment at their last visit had done so.
Moreover, 78.3% of subjects (54/69) achieved durable HBeAg seroconversion, with a somewhat higher percentage achieving seroconversion in the ADV-ADV group (37/45 subjects, 82.2%) than in the PLB-ADV group (17/24 subjects, 70.8%). Mean duration of durable HBeAg seroconversion for all age groups was 762 days (SD 371.2) in the ADV-ADV group and 643 days (SD 291.5) in the PLB-ADV group.

*HBs seroconversion*
Four subjects in the ADV-ADV group and 1 subject in the PLB-ADV group experienced HBsAg seroconversion during the study *(note: seroconversion occurred during ADV therapy at W180 for the patients in the PLB-ADV group).*



*<u>Rapporteur's comment</u>:*
*Among the 162 patients who entered open-label period, half discontinued prematurely from the study. Furthermore, at week 240, only 26 (16%) were still on ADV (most of the patients having stopped study drug due to insufficient virologic suppression).*
*After 48 weeks on ADV, mean change from baseline in HBV DNA was -3.43 in patients initially randomized to ADV and -3.69 in patients initially randomized to placebo. At the end of ADV treatment (W240 for ADV-ADV patients and W192 for PLB-ADV patients), mean change from baseline was almost similar in both groups: -5.87 $log_{10}$ copies/ml in ADV-ADV patients (n=7) and -5.41 $log_{10}$ copies/ml in PLB-ADV patients (n=9). For the few patients who remained on study drug during the 5 years study, it seems that receiving placebo during the first 2 years of the study was not "pejorative" in terms of virological response.*

*Overall, the study results, and notably HBV DNA and ALT endpoints, are hardly interpretable due to the fact that:*
*- sample size are limited (half of the patients completed the open-label period of the study)*
*- the open-label dataset is heterogenous (eg: exposure to ADV is heterogenous, on-treatment patients included some patients on ADV+LAM combination therapy, off-treatment patients included patients who stopped ADV for failure to treatment or, on the contrary, following seroconversion).*
*Nevertheless, we can note that around half of the paediatric patients failed to adequately suppress HBV DNA. For the remaining patients, virologic suppression (HBV DNA<1000 copies/ml) was mostly associated with HBeAg seroconversion since around 50% of paediatric patients had HBeAg seroconversion in this study; a rate close to the rate reported in long-term study in adults. Seroconversion was documented as durable for 78% of these patients. It was noteworthy that at the end of the double-blind period, 11% of adolescents patients had HBeAg seroconversion in both the ADV arm and the placebo arm at week 48. Spontaneous seroconversion was not documented in the open-label phase of the study since patients on placebo were switched to ADV after W48.*
*Very few (n=4) achieved the ideal endpoint of HBsAg seroconversion.*

*Comparison with adults data:*
*As a reminder, in HBeAg+ adults patients, long term data were available from study GS-98-437. At week 240, 42 patients (25%) were still on ADV; among them 39% had HBV DNA <1000 copies/ml and 66% had normalized ALT. Median change from baseline was -4.05 $log_{10}$ copies/ml.Over the course of the study, 48% of patients had confirmed HBeAg seroconversion and 2% (n=4) had HBs seroconversion.*

*To conclude, the long-term efficacy data are based on limited sample size and are presented for a heterogeneous population which makes the interpretation of the study results very difficult. As recognised by the MAH, ADV is not an optimal treatment for paediatric patients including adolescents patients. As a matter of fact, at the end of the 5 years study, more than 50% of patients were insufficiently suppressed and withdrawn from ADV. The long-term data further support the negative opinion previously given by the CHMP on the basis of the 48 weeks data of the study.*



**Clinical Virology findings**

**Cumulative Summary of Resistance Surveillance by Treatment and Previous HBV Treatment Exposure**

| | ADV-ADV (n = 115) | | | PLB-ADV (n = 58) | | |
|---|---|---|---|---|---|---|
| Category | Exp (n=64) | Naïve (n=51) | Total (n=115) | Exp (n=33) | Naïve (n=25) | Total (n=58) |
| Included in cumulative resistance surveillance[a] | 42 | 32 | 74 | 19 | 18 | 37 |
| Unable to genotype/missing data | 2[b] | 4 | 6 | 2 | 2[c] | 4 |
| Paired sequences for evaluation | 40 | 28 | 68 | 17 | 16 | 33 |
| No changes from baseline | 26 | 22 | 48 | 8 | 10 | 18 |
| Wild-type virus with changes from baseline at polymorphic sites | 12 | 5 | 17 | 7 | 5 | 12 |
| Developing changes from baseline at conserved sites | 2 | 1 | 3 | 2 | 1 | 3 |
| Developing mutations specific to ADV and/or LAM | 0 | 1 | 1 | 0 | 0 | 0 |

a Subjects were excluded from analysis if HBV DNA values were < 169 copies/mL at Week 240/last time point or if subject discontinued study drug but remained in the study.
b One subject in this category discontinued study drug at Week 44 with HBV DNA ≥ 169 copies/mL, the sample was not evaluated for genotypic changes since only Week 48 samples were to be tested.
c Two subjects in the category (treatment naïve in the placebo arm) discontinued prior to the open-label phase and were therefore not evaluated for genotypic changes.

Annual resistance surveillance was conducted for all subjects who had HBV DNA levels greater than or equal to the level of detection by PCR (≥ 169 copies/mL) during the open-label phase of the study. Among subjects originally randomized to receive ADV, the rtN236T ADV-associated resistance mutation developed in one treatment-naive subject.
Development of the rtN236T mutation occurred at Week 240 of ADV monotherapy and was associated with virologic breakthrough. The cumulative incidence of developing ADV associated resistance mutations (rtA181V/T or rtN236T) within the HBV pol/RT among subjects originally receiving ADV was 0% and 4% for the experienced and naïve populations, respectively.
None of the PLB-ADV subjects developed an ADV-associated resistance mutation while on ADV monotherapy.

Among the 32 subjects who received lamivudine in addition to adefovir, the rtA181T ADV and LAM-associated resistance mutation was observed in one subject at the last time point on therapy. Development of the mutation occurred at Week 204; the subject was originally randomized to the ADV arm and added LAM at week 144. In addition, one subject developed lamivudine-associated mutations (rtL180M and/or rtM204V/I). The subject was originally randomized to the ADV arm; lamivudine was added at Week 144, and the mutations were observed at Week 180 (last time point on study drug).
Nine treatment-experienced subjects (6 in the ADV-ADV group and 3 in the PLB-ADV group) entered the study with mutations associated with lamivudine (the rtM204V/I mutation [with or without rtL180M] and the rtA181A/T mutation). All 9 subjects responded to ADV therapy, with a median change from baseline in HBV DNA of 5.41 log10 copies/mL at the last time point on ADV monotherapy.

*Rapporteur's comment: As a reminder, no children developed rtA181T or rtN236T mutation over 48 weeks.*
*Only 1 paediatric patient developed ADV mutation (rtN236T) which occurred at Week 240 and was associated with breakthrough. One additional patient that received LAM+ADV developed rtA181T mutation (which is associated with resistance to LAM and reduced susceptibility to ADV). The low rate of emergence of mutation in this study has to be balanced with the small number of patients who remained on drug during the open-label phase of the study (more than half of the patients (n=87) had discontinued ADV before the end of Year 3 and only 26 were still on drug at the end of the study).*

**Safety Results:**

*Extent of exposure*
The mean duration of open-label exposure to ADV for all age groups was 98 weeks overall (90 weeks for subjects who received randomized ADV during the first 48 weeks of the study and 113 weeks in subjects who received randomized placebo during the first 48 weeks of the study).

*Summary of treatment-emergent AE*

| Adverse Event[a] Category, n (%)[b] | On-Trt OL ADV (DB ADV) (N=108) | On-Trt OL ADV (DB PLB) (N=54) | On-Trt OL Overall (N=162) | Off-Trt OL ADV (DB ADV) (N=108) | Off-Trt OL ADV (DB PLB) (N=54) | Off-Trt OL Overall (N=162) |
|---|---|---|---|---|---|---|
| With any AE | 75 (69.4%) | 47 (87.0%) | 122 (75.3%) | 60 (55.6%) | 31 (57.4%) | 91 (56.2%) |
| With any Grade 3 or 4 AE | 8 (7.4%) | 5 (9.3%) | 13 (8.0%) | 22 (20.4%) | 7 (13.0%) | 29 (17.9%) |
| With any Related AE | 10 (9.3%) | 6 (11.1%) | 16 (9.9%) | 16 (14.8%) | 5 (9.3%) | 21 (13.0%) |
| With any Grade 3 or 4 Study Drug-Related AE | 3 (2.8%) | 1 (1.9%) | 4 (2.5%) | 13 (12.0%) | 3 (5.6%) | 16 (9.9%) |
| With any SAE | 10 (9.3%) | 3 (5.6%) | 13 (8.0%) | 30 (27.8%) | 10 (18.5%) | 40 (24.7%) |
| With any Related SAE | 2 (1.9%) | 1 (1.9%) | 3 (1.9%) | 16 (14.8%) | 3 (5.6%) | 19 (11.7%) |
| With any AE that Caused Permanent Discontinuation From Study Drug | 2 (1.9%) | 0 | 2 (1.2%) | 0 | 0 | 0 |
| With any Change in Dose or Temporary Study Drug Interruption | 3 (2.8%) | 1 (1.9%) | 4 (2.5%) | 0 | 0 | 0 |

The overall frequency of AEs during the open-label period was 69.4% of subjects in the ADV-ADV group and 87.0% of subjects in the PLB-ADV group while on treatment. While off-treatment, the overall frequency of AEs was 55.6% in the ADV-ADV group and 57.4% in the PLB-ADV group.
The most frequently reported AEs while subjects were on-treatment were pharyngitis (16.0%), nasopharyngitis (12.3%), abdominal pain (11.7%), headache (9.3%), bronchitis (6.2%), rash (6.2%), and tonsillitis (5.6%). The most frequently reported AEs while subjects were off-treatment were hepatitis (includes hepatic flares and exacerbations of hepatitis, 14.8%), pharyngitis (8.6%), pyrexia (8.0%), nasopharyngitis (6.2%), and increased ALT (5.6%).
No new or unexpected AEs were identified. The events observed in the Weeks 48−240 were similar to those observed in the first 48 weeks of the study. Of note, **a total of 46 subjects (28.4%) experienced at least one AE related to hepatic status or function during the open-label treatment period.**

The incidence of Grade 3 or 4 AEs was 7.4% in the ADV-ADV group and 9.3% in the PLB-ADV group while subjects were on-treatment and 20.4% in the ADV-ADV group and 13.0% in the PLB-ADV group while subjects were off-treatment. Serious adverse events were more common while subjects were off-treatment than on-treatment (on-treatment: ADV-ADV: 9.3%; PLB-ADV: 5.6%; off-treatment: ADV-ADV: 27.8%; PLB-ADV: 18.5%). This was related to the incidence of posttreatment exacerbation of hepatitis B, defined a priori in the protocol as an SAE. Other SAEs in subjects who were on-treatment included alcohol poisoning (1.2%), joint injury (1.2%), and depression (1.2%).

Two subjects in the ADV-ADV group were withdrawn from the study due to AEs during the open-label phase while on-treatment; one had moderate depression that was an SAE and considered to be study drug related and the other was withdrawn due to a moderate rash that was considered to be related to study drug.

With the exception of ALT and AST, no marked laboratory abnormality was reported in more than 8% of subjects in either treatment group during the open-label period. Of note, Grade 3/4 increased creatine kinase was reported in 4.6% of patients in the ADV-ADV group and in 7.4% of patients in the PLB-ADV group while on-treatment.

*Adverse events of special interest*
- Hepatic adverse events:
A total of 46 subjects (28.4%) experienced at least one AE related to hepatic status or function during the open-label treatment period, most being hepatic flares reported off-treatment.
Hepatic flares were defined as a) serum ALT > 2 × study baseline and > 10 × ULN, or, b) an ALT 1-grade shift or ALT 2× previous value and total bilirubin > 2.5 mg/dL or change from study baseline in total bilirubin = 1.0 mg/dL or change from study baseline in PT > 2 seconds or serum albumin < 3.0 g/dL or change from study baseline in serum albumin ≤ −1.0 g/dL.

As would be expected, hepatic flares were observed in a much higher proportion of subjects who were off ADV treatment than those who were on ADV treatment. Four subjects (2.5%) who were on-treatment (3 (2.8%) ADV-ADV subjects and 1 (1.9%) PLB ADV subject) and **31 subjects (19.6%) who were off-treatment** (ADV-ADV: 23.1%; PLB-ADV: 11.1%) had changes in laboratory values that met the definition of a hepatic flare.
Most hepatic flares were limited to increases in ALT without concurrent confirmed abnormalities in PT, albumin, or bilirubin, except for 3 patients (2 had increased in total bilirubin and 1 had grade 1 abnormalities in PT). None of the hepatic flares were associated with decompensation.

- Renal adverse events:
No AEs suggested adverse effects on renal function. In addition, there were **no subjects with confirmed phosphorous < 2 mg/dL, or creatinine clearance (Schwartz and/or Cockcroft & Gault) < 50 mL/min.**
However, more subjects receiving ADV-ADV (15.7%) on-treatment had a confirmed increase in creatinine of 0.3 mg/dL above the ADV baseline value compared to PLB-ADV subjects (13.0%). This difference was also seen in subjects who were off-treatment (ADV-ADV: 19.4%; PLB-ADV: 7.4%).

| Clinical Laboratory Abnormality | On-Trt OL ADV (DB ADV) (N=108) | On-Trt OL ADV (DB PLB) (N=54) | On-Trt OL Overall (N=162) | Off-Trt OL ADV (DB ADV) (N=108) | Off-Trt OL ADV (DB PLB) (N=54) | Off-Trt OL Overall (N=162) |
|---|---|---|---|---|---|---|
| Number of Subjects With Confirmed Increase in Creatinine of 0.3 mg/dL above ADV BL, n (%) | 17 (15.7%) | 7 (13.0%) | 24 (14.8%) | 21 (19.4%) | 4 (7.4%) | 25 (15.4%) |
| Number of Subjects With Confirmed Increase in Creatinine of 0.5 mg/dL above ADV BL, n (%) | 2 (1.9%) | 2 (3.7%) | 4 (2.5%) | 4 (3.7%) | 1 (1.9%) | 5 (3.1%) |
| Number of Subjects With CLcr Schwartz < 80 mL/min, n (%) | 1 (0.9%) | 2 (3.7%) | 3 (1.9%) | 0 | 1 (1.9%) | 1 (0.6%) |
| Number of Subjects With Combined Creatinine Clearance (Schwartz and Cockroft & Gault) < 80, n (%) | 3 (2.8%) | 2 (3.7%) | 5 (3.1%) | 1 (0.9%) | 1 (1.9%) | 2 (1.2%) |

ADV baseline was defined as the day of first dose of ADV.

- Adverse events related to appetite

No subject had an AE related to decreased food intake or weight loss. Two (1.2%) on-treatment ADV-ADV subjects and 2 (1.2%) off-treatment subjects (one ADV-ADV and one PLB-ADV) had anorexia, that were judged as unrelated to study drug.

In general, the **height, weight, and BMI Z-scores for subjects in both treatment groups were lower than Z-scores for the reference population at Week 240 for subjects who were on-treatment.** However, Z-scores for height and weight for subjects in both treatment groups were **similar to those for the reference population for subjects who were off-treatment at Week 240.** There were statistically significant differences in height and weight between the two treatment groups at Week 240 only ($p = 0.017$ and $p = 0.048$, respectively). However, very small numbers of subjects were included in this calculation at Week 240 (ADV-ADV: 5; PLB-ADV: 8). No significant differences in height or weight were seen at any other time point for both treatment groups while subjects were on-treatment. There was a statistically significant difference in weight between the two treatment groups for subjects who were off-treatment at Week 192 only ($p = 0.019$). There was a statistically significant difference in BMI between the two treatment groups at Week 48 ($p = 0.005$). No significant differences in BMI were seen at any other time point for both treatment groups while subjects were on-treatment.

There was a statistically significant difference in BMI between the two treatment groups for subjects who were off-treatment at Week 144 ($p < 0.001$).

*<u>Rapporteur's comment</u>:*

*No unexpected adverse events were reported during the open-label period of the study. However, a notable high rate of hepatic flares post-treatment was reported in this paediatric study. Indeed, around 20% of study patients experienced hepatic flares following discontinuation of ADV (less than 10% had exacerbation of hepatitis post-treatment in adults studies -437 and -438). Fortunately, none were associated with decompensation in this study. Nevertheless, the high rate of hepatic flares reported in the paediatric population is of concern.*

*Confirmed increase in creatinine of 0.5mg/dl was reported in 2.5% of patients on-treatment and 3.1% of patients off-treatment. None were associated with renal adverse events in this study.*

*As for other nucleoside analogs, particular caution should be given to laboratory abnormalities which might be associated with mitochondrial toxicity. Of note, grade 3/4 increases in creatinine kinase were reported in around 5% of patients in this study but none were associated with marked clinical events.*

*Finally, the long-term safety data on ADV do not allow dispelling the fears as regards the potential impact of ADV on appetite-related disorders and growth. As a matter of fact, BMI Z-scores were negative in both the ADV-ADV and PMB-ADV groups at W240 indicating that patients had lower BMI at the end of the study than typical for their age and gender.*

## B. ASSESSMENT OF SUPPLEMENTAL DATA RELATED TO FU2 028.7

In accordance with FU2 028 (FUM 9), additional analyses of the presence of basal core promoter and pre-core mutations at baseline among hepatitis B e antigen (HBeAg) positive paediatric patients were conducted in Study GS-US-103-0518. The purposes of these analyses were to assess whether the presence of these mutations can predict the likelihood of HBeAg seroconversion, and of whether these mutations are related to treatment response. These results are still being gathered. However, preliminary data has shown that the baseline incidence of basal core promoter mutations was significantly associated with confirmed HBeAg seroconversion, but the baseline incidence of precore mutations was not. Poster 360 (Chappell et al, 2009) details the preliminary data (please see in annex). Final results from these additional analyses will be shared when available.

*Rapporteur's comment:*
*The clinical impact of pre-existing basal core promoter and precore mutations at baseline on the likelihood of seroconversion will be discussed in the light of the final data.*

### *MAH's conclusions on the Benefits and Risks*

Based on the efficacy and safety findings of Study GS-US-103-0518, the sponsor concludes that ADV provides a treatment option in 12–17-year-old patients with CHB. However, it is not an optimal treatment as a sizable proportion of adolescent patients failed to achieve HBV DNA suppression <1000 copies/mL. Additionally, given the failure to suppress HBV DNA adequately in a majority of the 2–6- and 7–11-year-old subjects and the attendant risk of genotypic adefovir resistance, ADV treatment presents an uncertain risk-benefit ratio in patients less than 12 years of age. Although some younger patients may derive virologic or serologic benefit, the majority of these subjects would be at risk for emergence of resistance due to the failure of ADV to suppress HBV DNA adequately. This would limit future treatment options. It would therefore seem prudent to defer treatment with ADV until an age at which adequate virologic suppression would be expected.
Based on the data presented in this application, no changes to the national prescribing information are proposed to support the use of Hepsera in pediatric patients.

## III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

In accordance with Article 46 of Regulation (EC) n°1901/2006, GILEAD is submitting the final study report for the paediatric study GS-US-103-0518. The 48 weeks double-blind data from this study were previously assessed by the CHMP in the setting of the extension variation II30, submitted by the MAH to extend the indication of Hepsera to adolescents above 12 years of age. In the light of the 48 weeks data, the CHMP considered that the clinical study did not provide convincing arguments to consider that the use of ADV might be more beneficial than deleterious in adolescents. In view of the major objections raised by the CHMP, the MAH decided not to pursue the extension of indication. As such, HEPSERA is not indicated in adolescents in Europe.

As a matter of fact, and as a general consideration, it is noteworthy that since the arrival of drugs with both high potency and high genetic barrier, tenofovir and entecavir, the place of drugs such as adefovir and lamivudine has been quite marginalised in the therapeutic armamentarium, whatever the situation.

The long-term data presented in the current submission do not allow reversing the previous conclusion. The available data do not support a positive benefit/risk ratio for Hepsera in paediatric patients, including adolescents. As a matter of fact, most of the patients, including adolescents, were insufficiently suppressed with HEPSERA. In terms of safety, the high rate of hepatic flares reported in this study following discontinuation of ADV is of concern. Increase in creatinine and CPK levels as well as the fears as regards a potential impact on growth are also causes for concern for the paediatric patients.

HEPSERA SPC currently reflects the 48 weeks data of study GS-US-103-0518. The wording aimed at discouraging the off label use of adefovir in the paediatric population.
The long-term data should also be shortly reflected. We would be in favour of replacing the terms "due to insufficient data" by "due to the limitations of the available data on safety and efficacy", insofar that insufficient might appear somewhat contradictory when considering that long term data are now available. The message should that the available data as such fail to provide sufficient degree of reassurance in terms of efficacy and safety.

We propose to revise the SPC as follows:

4.2: *Children and adolescents:* Hepsera is not recommended for use in children below the age of 18 years due to ~~insufficient~~ **the limitations of the available** data on safety and efficacy (see section 5.1).

5.1
*Paediatric population:* The efficacy and safety of a daily dose of 0.25 mg/kg to 10 mg adefovir dipivoxil in children (aged from 2 to < 18 years) was examined in a double-blind, randomised, placebo-controlled study in 173 paediatric patients (115 on adefovir dipivoxil, 58 on placebo) who had HBeAg positive chronic hepatitis B, serum ALT levels ≥ 1.5 x upper limit of normal (ULN) and compensated liver disease. At week 48, in children aged 2 to 11 years old, no statistically significant difference was observed in the proportions of patients that achieved the primary endpoint of serum HBV DNA < 1,000 copies/ml and normal ALT levels between the placebo arm and the adefovir dipivoxil arm. In the adolescent population (n=83) (aged from 12 to < 18 years), significantly more patients treated with adefovir dipivoxil achieved the primary efficacy endpoint and obtained significant reductions in serum HBV DNA (23 %) compared to placebo-treated patients (0 %). However, the proportions of subjects who achieved HBeAg seroconversion at week 48 were similar (11 %) between the placebo arm and the adefovir dipivoxil 10 mg arm in adolescent patients.

Overall, the safety profile of adefovir dipivoxil in children was consistent with the known safety profile in adult patients. However, a signal towards a higher rate of decreased appetite and/or food intake was observed in the adefovir arm as compared to the placebo arm. At week 48 and 96, mean changes from baseline in weight and BMI Z scores tended to decrease in adefovir dipivoxil-treated patients. ~~No long-term safety data or long-term resistance data are available with adefovir dipivoxil in children.~~
**At Week 48, all placebo-treated subjects who did not exhibit HBeAg or HBsAg seroconversion, plus all ADV−treated subjects, were offered the opportunity to receive open-label ADV from study week 49**

**through to week 240. A high rate (30%) of hepatic flares were reported following discontinuation of adefovir dipivoxil during the 3 years open label phase of the study. Furthermore, for the few patients who remained on drug at week 240 (n=12) BMI Z score was lower than typical for their age and gender. Very few patients developed adefovir-associated mutations up to 5 years; however, the number of patients who remained on drugs above week 96 was limited.**

**Due to their limitations,** ~~T~~the clinical data available ~~are insufficient~~ **do not allow** to draw definitive conclusions on the benefit/risk ratio of the adefovir treatment in children with chronic hepatitis B (see section 4.2)".

Finally, the MAH acknowledged that HEPSERA is not an optimal option for paediatric patients in view of its low potency in this population. This consideration of course also holds true for adults. **Hepsera can no longer be regarded as an optimal first line monotherapy besides tenofovir or entecavir should be reflected in the SPC.**

Fully acknowledging that it is out of the scope of this FUM, the Rapporteur would nevertheless like to take the opportunity of this procedure, to ask the applicant to make a proposal for a revision of the indication. The following concept should be introduced "when the use of an alternative antiviral agent with a higher potency and a higher genetic barrier is not available or appropriate and the need to combine the drug with a second agent without cross-resistance to adefovir in patients with decompensated liver disease."

- **Recommendation**

☒ **Fulfilled –**

**The MAH should commit to submit type II variation to reflect the long-term data from study GS-US-103-0518 in paediatric patients and to revise the indication to reflect the fact that Hepsera can no longer be regarded as a first line monotherapy for the treatment of HBV-infected patients.**

**FUM 28:** The MAH should submit the final results from the analyses of the incidence of basal core promoter and precore mutations at baseline among HBeAg paediatric patients when available.

Poster Number

**360**

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# Preliminary Analysis of the Incidence of Basal Core Promoter and Precore Mutations at Baseline Among HBeAg Positive Pediatric Patients with Durable HBeAg Seroconversion and Active Viral Replication

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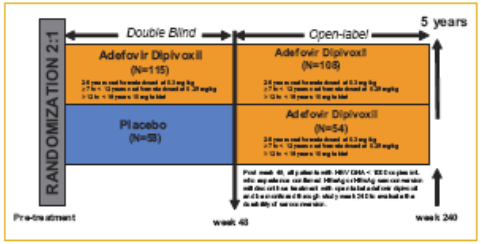
## Introduction

- The most common mutations in the basal core promoter (BCP) region of the HBV genome are dual mutations A1762T and G1764A, which down-regulate HBeAg production
- The predominant mutation in the precore (PC) region (G1896A) creates a stop codon in the reading frame, thus preventing production of HBeAg

Figure 1. GS-US-103-0518 study design




## Objective

- To determine the incidence of BCP and PC mutations (A1762T, G1764A and G1896A) at baseline among HBeAg+ pediatric patients enrolled in a phase 3 study of adefovir dipivoxil (ADV)
- To assess the association of baseline BCP and PC mutations and subsequent HBeAg seroconversion

## Methods

- HBeAg+ pediatric patients (aged 2 to <18 years) were enrolled in a placebo-controlled randomized study of ADV [GS-US-103-0518]
- Population di-deoxy sequencing of serum HBV from the HBeAg region was conducted
  - A 300 base-pair fragment of the HBeAg region was amplified for evaluation for all patients at baseline
  - A subset of patients with confirmed HBeAg seroconversion and HBV DNA ≥ 1000 copies/mL while off-treatment was evaluated
  - Assay allows detection of mixtures present at ≥ 25% of viral quasi-species population
- Two-sided Fisher exact test was used to test the association of baseline BCP and PC mutations with confirmed seroconversion
- Serum HBV DNA levels were determined by Roche COBAS TaqMan assay (LLOQ = 169 copies/mL; 29 IU/mL)

## Results

Table 1. Baseline demographics GS-US-103-0518 patients

| Baseline characteristic | ADV-ADV (n=115) | PLB-ADV (n=58) |
|---|---|---|
| HBeAg positive | 113 (98%) | 57 (98%) |
| Mean age (years) – Range | 10.8 (2-17) | 10.7 (2-17) |
| Prior chronic hepatitis B treatment | 64 (56%) | 33 (57%) |
| Mean HBV DNA ($log_{10}$ copies/mL) | 8.74 | 8.67 |
| Mean ALT (U/L) | 111 | 99 |
| Mean ALT as a multiple of ULN | 2.9 | 2.6 |

Figure 2. Percentage of BCP and PC mutations observed at baseline

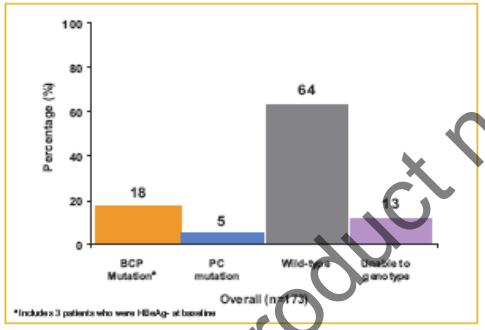



Table 2. Mutational patterns at baseline among patients with mutations in BCP and PC region

| Mutational pattern observed | Region | Number of patients (n=40) |
|---|---|---|
| A1762T, G1764A | BCP | 14 |
| A1762A/T, G1764G/A | BCP | 10 |
| A1762T, G1764A/G | BCP | 1 |
| A1762T | BCP | 2 |
| A1762A/T | BCP | 2 |
| A1762A/C | BCP | 1 |
| G1764A/G | BCP | 1 |
| G1896G/A | PC | 9 |

Figure 3. BCP mutations at baseline were associated with confirmed HBeAg seroconversion

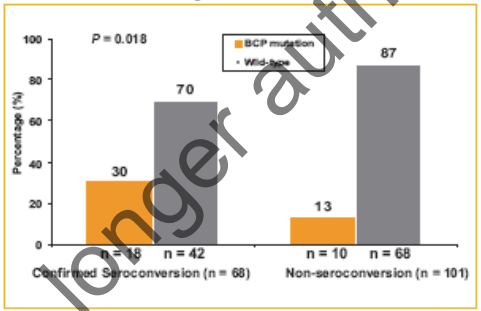



Figure 4. PC mutations at baseline were not associated with confirmed HBeAg seroconversion

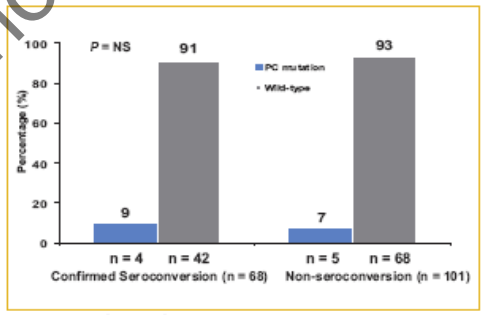



Table 3. BCP and PC mutational patterns post baseline among patients with confirmed HBeAg seroconversion and HBV DNA ≥ 1000 copies/mL while off treatment

| Mutational pattern observed | Region | Number of patients (n=37)a |
|---|---|---|
| A1762T, G1764A | BCP | 10 |
| A1762A/T, G1764G/A | BCP | 3 |
| A1762T, G1764A, G1896G/A | BCP and PC | 1 |
| A1762T | BCP | 2 |
| G1764T | BCP | 1 |
| G1896A | PC | 3 |
| G1896G/A | PC | 2 |
| Wild-type | BCP and PC | 13 |

a PCR amplification failed for 2 patients

Table 4. Paired baseline and post-baseline analysis for patients with confirmed HBeAg seroconversion and HBV DNA ≥ 1000 copies/mL while off treatment

| Changes in mutational pattern observed from baseline | Number of paired observations (n=32) |
|---|---|
| A1762A/T, G1764G/A → A1762T, G1764A | 5 |
| A1762A/T → A1762T, G1764A | 1 |
| A1762A/C → A1762T | 1 |
| A1762A/T, G1764G/A → Wild-type | 1 |
| A1762A/T → Wild-type | 1 |
| A1762T, G1764A → A1762T, G1764A, G1896G/A | 1 |
| A1762T, G1764A → A1762T, G1764A | 1 |
| A1762T → A1762T | 1 |
| Wild-type → A1762T, G1764A | 2 |
| Wild-type → A1762A/T, G1764G/A | 2 |
| Wild-type → G1896A | 3 |
| Wild-type → G1896G/A | 2 |
| Wild-type → Wild-type | 11 |

## Conclusions

- Among this population of HBeAg+ pediatric patients (n=173), baseline incidence of basal core promoter (BCP) mutations was significantly associated with confirmed HBeAg seroconversion.
  - Baseline incidence of precore (PC) mutations was not found to be significantly associated with HBeAg seroconversion.
  - A variety of BCP and PC mutational patterns were observed at baseline indicating that the mutations pre-exist among patients with HBeAg+ disease.
- A subset of patients (n=11) remained wild-type after confirmed HBeAg seroconversion indicating that other mechanisms exclusive of BCP or PC mutations are also associated with HBeAg seroconversion.

## Acknowledgment

1. Ken Peschell for statistical support and critical review of the data.