24 July 2014
EMA/563133/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Baraclude

International non-proprietary name: ENTECAVIR

Procedure No. EMEA/H/C/000623/II/0041

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADV	adefovir
ADVr	adefovir resistance
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(TAU)	area under the concentration-time curve in 1 dosing interval
BSA	body surface area
CLT/F	apparent total body clearance
CLT/F/BSA	apparent total body clearance normalized to body surface are
CLT/F/kg	apparent oral clearance normalized to body weight
CHB	chronic hepatitis B
Cmax	peak plasma concentration
Cmin	trough observed plasma concentration
CSR	clinical study report
DNA	deoxyribonucleic acid
ETV	entecavir (BMS-200475; Baraclude)
ETVr	entecavir resistance
EU	European Union
HA	Health Authority
HAP	height for age percentile
HAZ	height for age Z score
HBeAg	hepatitis B e antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
LOQ	limit of quantitation
LVD	lamivudine
LVDr	lamivudine resistance
MAH	marketing authorization holder
NC = F	non-completer = failure

PCR	polymerase chain reaction
PDCO	Paediatric Committee
PK	pharmacokinetic(s)
PPD	pharmacokinetic-pharmacodynamic
PPK	population pharmacokinetic(s)
QD	Once daily
RespMax	maximum change from baseline
SAE	serious adverse event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
TDay50	time to half maximal response
TDF	tenofovir
ULN	upper limit of normal
US	United States
WAP	weight for age percentile
WAZ	weight for age Z score

Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 6 November 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Baraclude	ENTECAVIR	See Annex A

The following variation was requested

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include treatment of chronic HBV infection in paediatric patients from 2 to <18 years of age with compensated liver disease and evidence of active viral replication and persistently elevated serum ALT levels.

Consequently, the MAH proposed the update of sections 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

The variation proposed amendments to the SmPC and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0125/2014 on the agreement of a paediatric investigation plan (PIP).

The PIP [P/0125/2014] was completed and the PDCO issued an opinion on compliance for the PIP [P/0125/2014].

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Pierre Demolis

Submission date:	06 November 2013
Start of procedure:	22 November 2013
Rapporteur's preliminary assessment report circulated on:	13 January 2014
Co-Rapporteur's preliminary assessment report circulated on:	20 January 2014
Joint Rapporteur's updated assessment report circulated on:	14 February 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 February 2014
MAH's responses submitted to the CHMP on:	21 May 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	04 July 2014
PRAC RMP advice and assessment overview adopted by PRAC Joint	10 July 2014
Rapporteur's updated assessment report on the MAH's responses circulated on:	18 July 2014
CHMP opinion:	24 July 2014

2. Scientific discussion

Baraclude contains entecavir, a cylcopentyl guanosine nucleoside analogue that was approved in the European union (EU) in 2006 for the treatment of CHB in adults. The MAH applies for an extension of indication to include treatment of chronic HBV infection in paediatric patients from 2 to <18 years of age with compensated liver disease and evidence of active viral replication and persistently elevated serum ALT levels.

More than 360 million persons worldwide (6% of the world population) are chronically infected by the hepatitis B virus (HBV). Although the incidence of HBV infection has dramatically declined since the implementation of universal immunization programs in several countries and blood-donor screening, a significant number of children are still infected each year, often developing chronic infection and requiring appropriate follow-up.

The ultimate clinical goal of treatment of chronic HBV is the prevention of cirrhosis, hepatocellular carcinoma and end-stage liver disease. The proximate goal is HBsAg seroconversion, which is not achievable in most cases. When this situation is not achieved, sustained off-therapy suppression of viral replication (undetectable HBV-DNA) along with HBeAg seroconversion, which has been associated with a decreased risk of hepatocellular carcinoma. In the absence of off-therapy viral suppression, suppressed HBV-DNA with long term antiviral therapy is the next desirable endpoint. Reduction of viremia leads to decreased liver inflammation, reducing the risk of disease progression.

Despite a rather benign course of chronic hepatitis B (CHB) during childhood and adolescence, 3–5% and 0.01–0.03% of chronic carriers develop cirrhosis or hepatocellular carcinoma (HCC), respectively, before adulthood . According to recently published ESPHGAN (European Society of Pediatric Gastroenterolgy, Hepatology and Nutrition) guidelines, pharmacological treatment of children with chronic hepatitis B infection is indicated in patients with persistently elevated ALT (>6 months) that

are (a) HBeAg+ and have HBV-DNA levels >20,000 IU/ml or (b) HBeAg- with HBV-DNA >20,000 IU/mL, provided that liver biopsy shows moderate/severe inflammation/fibrosis, or if there is a family history of HCC. The first line treatment is an alfa-interferon, and in the case that sustained response is not reached, treatment with a nucleos(t)ide analogue is recommended. Furthermore, nucleos(t)ide analogue treatment is recommended in the rare patients with decompensated liver disease (Sokal et al, J Hepatol 2013).

Whereas there are a number of drugs indicated for the use against chronic hepatitis B infection in adults in Europe, only tenofovir presently has a paediatric indication, extending from 12 years and upwards.

2.1. Introduction

The ETV paediatric development program comprised of 2 studies. Study AI463028 is a Phase 2b, single-arm, open-label study to assess the pharmacokinetics (PK), safety, tolerability, and preliminary efficacy of ETV in paediatric subjects with HBeAg-positive CHB. Study AI463189 is a Phase 3 comparative, randomized, double-blind, placebo-controlled, multicenter study that compares the efficacy and safety of ETV with placebo in nucleoside-naive subjects with HBeAg-positive CHB.

The application submitted is aimed to extend the indication to paediatric patients who are nucleoside-naive with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB) between 2 to < 18 years of age and the paediatric studies described were provided in support of this application. The design of both paediatric studies includes long-term follow up for a total of 5 years (including on-treatment and post-study drug periods).

2.2. Non-clinical aspects

2.2.1. Introduction

Entecavir is phosphorylated in a variety of cell types to the active triphosphate form. By competing with the natural substrate deoxyguanosine triphosphate, entecavir-triphosphate is a functional inhibitor of priming of the HBV polymerase, reverse transcription of the negative strand DNA synthesis and synthesis of the positive strand HBV DNA of the viral polymerase. Entecavir is approved for the treatment of chronic hepatitis B infection in adults with evidence of immune or histologically active disease. The present application concerns the use of entecavir in paediatric patients with chronic hepatitis B infection, aged 2 to < 18 years.

In support of this new indication the applicant has submitted two juvenile toxicity studies in juvenile rats, DN05055/930018624 and DN06022/930022680. The ERA has also been briefly updated.

2.2.2. Toxicology - juvenile animals

Study DN05055/930018624 was a non-GLP dose range finding study, the parameters studied and findings are summarized below.

In the pivotal GLP-compliant toxicity study DN06022/930022680, the following parameters were studied: clinical signs, body weight, food consumption, sexual maturation and behavioural endpoints including functional observational battery, acoustic startle habituation, water maze learning/memory and motor activity, clinical pathology, organ weights, histopathology, estrous cyclicity, sperm endpoints, fertility indices and reproductive function.

Table 1. Summary of the toxicity studies performed with entecavir in juvenile rats.

Study number/ Testing facility	Species/ Strain Number/ Sex/Group	Route/Dose/ Duration (mg/kg/day)	Major Findings
DN05055/930 018624 CRL HOR Non-GLP/DRF	Crl:CD(SD) rats 20 pups/sex/ dose group excluding toxicokinetic dose groups	Oral gavage PND: 4-42 M: 0, 1, 3, 10 F: 0, 10, 20, 40 Controls: 1% Avicel /0.25% Methocel	Parameters studied: survival, clinical signs and body weights NOEL: 3 mg/kg in males, not identified in females. Mortality: Males, at 10 mg/kg, 4 rats dead on PND 6-11. Females, 4, 15 and 35 rats dead on PND 7-22 at 10, 20, and 40 mg/kg, respectively. Some of these were related to intubation trauma. Due to excessive toxicity, the 40 mg/kg dose was discontinued after approximately 2 weeks. Clinical observations: Females, at 20 and 40 mg/kg, dehydration, abdominal swelling, decreased body weight gain (11-20% compared to controls), body weight loss. Kinetics: Mean $AUC_{(0-24h)}$ values were 12,000, 17,800, and 44,800 ng∗h/mL on PND 7 at 10, 20, and 40 mg/kg/day, respectively. On PND 28, AUC values were 4,240 and 9,326 ng∗h/mL at 10 and 20 mg/kg, respectively (no data at 40 mg/kg/day on PND 28).
DN06022/930 022680 CRL HOR GLP	Crl:CD(SD) rats 100 pups/sex/ dose group excluding toxicokinetic dose groups	Oral gavage PND: 4-80, 3 months recovery period M and F: 0, 0.1, 1, 10 Controls: water	NOAEL: 1 mg/kg/day Apart from below, all other parameters were unaffected by treatment. Mortality: At 10 mg/kg, 3 males and 1 female. Body weight: Decreased weight (14% of controls at PND 80) and food consumption (10% of controls at PND 80) in males at 10 mg/kg. Clinical pathology: In males, increased aspartate aminotransferase and alanine aminotransferase in males (2.3-2.5 X controls) at 10 mg/kg, slight increase in sorbitol dehydrogenase in females and males. Organ weights: At 10 mg/kg, reduced absolute prostate weights (22% compared to controls at

Study number / Testing facility	Species / Strain Number / Sex / Group	Route / Dose / Duration (mg / kg / day)	Major Findings
			PND 80, not reversible). Histopathology: slight (grade 2/5) skeletal muscle myopathy, multifocal degeneration / regeneration of individual muscle fibers in the hind limb muscle in 1 male at 10 mg/kg PND 81. Behavioural evaluations: In males and females, at 10 mg/kg, a reduced acoustic startle response (45-52% compared to controls) was noted during recovery period (not reversible).

PND = postnatal day

Toxicokinetic data

Table 2. Entecavir exposure in rats on postnatal day 7 and 28 (study DN05055/930018624).

Male Rats				
Dose (mg/kg/day)	PND 7		PND 28	
	Cmax (ng/mL)	AUC_{0-24}[a] (ng·h/mL)	Cmax (ng/mL)	AUC_{0-24} (ng·h/mL)
1	164	1200	151	416
3	616	3710	470	1380
10	1770	12800	1330	4880
Female Rats				
Dose (mg/kg/day)	PND 7		PND 28	
	Cmax (ng/mL)	AUC_{0-24} (ng·h/mL)	Cmax (ng/mL)	AUC_{0-24} (ng·h/mL)
10	2050	12000	1530	4240
20	2470	17800	2840	9326
40	4520	44800	NA[b]	NA

[a] $AUC_{(0-24)}$ = Calculated from time zero to the time of last measurable concentration (24 h); [b]NA = Not available. Female rats at 40 mg/kg/day were discontinued from study prior to PND 28.

Table 3. Entecavir exposure in rats on postnatal day 7, 28 and 75 (study DN06022/930022680).

Parameter	Postnatal Day	BMS-200475 Dose (mg/kg/day)					
		0.1		1		10	
		Male	Female	Male	Female	Male	Female
Cmax (ng/mL)	7	13.8	12.5	120	120	1,160	1,190
	28	36.7	10.4	89.8	119	992	1,350
	75	5.98	4.50	78.5	55.9	694	557
AUC (0-24) (ngxh/mL)	7	103	85.4	974	903	11,800	10,800
	28	63.8	34.7	384	416	3,470	3,800
	75	26.0	14.9	273	172	4,520	1,730

2.2.3. Ecotoxicity / environmental risk assessment

Since the extended indication might lead to an increased exposure to the environment, an updated ERA was submitted.

Phase 1 calculation, including paediatric population

Table 4. Predicted environmental concentration (PEC)

DOSEai	Maximum daily dose	1 mg/day
Fpen	Market Penetration - Default (1%)	0.01
WasteWInhab	Amount of wastewater per inhabitant per day	200 L/Inhab-day
Dilution	Default value	10
$PEC_{surfacewater}$	Predicted environmental concentration in surface water	---

$PEC_{surfacewater}$ = (1 mg/day * 0.01) / (200 L/Inhab-day * 10)

$PEC_{surfacewater}$ = 0.000005 mg/L

$PEC_{surfacewater}$ = 0.005 µg/L (below 0.01 µg/L action level)

Persistence, Bioaccumulation and Toxicity

An experimentally determined (Shake Flask method) log Kow of -0.82 at pH 7.1 was included in previous submissions of entecavir. Additionally, log Kow values of -1.3 and -1.1 have been reported at pH 2.1 and pH 9.4, respectively.

2.2.4. Discussion on non-clinical aspects

Assessment of paediatric data on non-clinical aspects

In the pivotal toxicity study in juvenile animals, the rats were dosed by oral gavage at 0.1, 1 and 10 mg/kg/day between postnatal day 4-80, followed by a 3 months recovery period. The main findings concerned the male rats at 10 mg/kg and included increased aspartate aminotransferase and alanine aminotransferase levels (2.3-2.5 times of controls) and reduced absolute prostate weights (22% compared to controls). Further, slight skeletal muscle myopathy was noted in one male only, described as multifocal degeneration and regeneration of individual muscle fibres in the hind limb. Of these findings, only the reduced prostate weight was not reversible during the 3 months recovery period. These effects are not exclusive for juvenile rats but seen also in previous studies in adult rats, studies submitted and assessed in relation to the adult indication of entecavir. Liver and testis toxicity appeared to be more specific in adult rats, whereas toxicity of the prostate noted in the juvenile rats was seen primarily in adult dogs and not in adult rats. The changes in prostate weight in the juvenile animals are considered secondary to the body weight reductions.

A reduced acoustic startle response (45-52% compared to controls) was noted at 10 mg/kg in both male and female during the recovery period, but curiously not during the treating period. The clinical significance of this finding is unclear, but has been included in section 5.3 of the SmPC. Based on these results the No Observed Adverse Effect Level (NOAEL) for males and females was 1 mg/kg/day.

Review of the toxicokinetic data reveal that the systemic exposure decreases significantly with duration of treatment, across all dose groups. In males, it decreases by a factor of 2.5 to 4, while in females it was reduced by 5-6 times. This might be due to an increased maturation of the developing metabolic systems. It seems to be a gender difference between females and males also in adult rats, females showed lower AUC-values and males. The comparisons below refer to the Day 75 values (being the lowest values reported).

The exposure in male rats at 10 mg/kg, 4520 ng*h/mL, gives a margin to clinically relevant exposure of approximately 200, based on 18.77 ng*h/mL, mean AUC in paediatric human subjects given 0.015 mg/kg/day entecavir for 2 weeks. At NOAEL, 1 mg/kg, the margin is approximately 10 males and females combined. In adult male rats skeletal muscle myopathy was seen 0.3-0.6 mg/kg, where the AUC levels of 168-408 ng*hr/mL generates a margin to clinically relevant exposure of approximately 10-20. It can thus be concluded that based on these studies, the juvenile rat is not more sensitive to entecavir exposure than to the adult rat.

The rats were evaluated from postnatal day 4-80, consequently the corresponding early (2 to 12 years) and adolescent (12 to 18 years) stages of development in humans is considered covered.

An impurity, BMS-200727 (< 0.03%), is mentioned in the Toxicology Tabulated Summary. Specific studies concerning impurities have not been conducted and are not considered necessary as BMS-200727 was present in the batches used in the studies submitted.

ERA

As the calculated $PEC_{surfacewater}$ value is <0.01 µg/L, no Phase II assessment is necessary in accordance with the "*Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use*" EMEA/CHMP/SWP/4447/00. As experimentally determined (Shake Flask method) log Kow is ≤ 4.5, entecavir does not meet the screening criteria for bioaccumulation. Entecavir is hence not considered a PBT substance.

2.2.5. Conclusion on the non-clinical aspects

No new findings relevant for clinical safety assessment were observed in juvenile rats at an

exposure well over clinical exposure. A reduced acoustic startle response was noted during the recovery period, but not during the treating period, in both male and female rats at 10 mg/kg. The clinical significance of this finding is unclear, but is mentioned in section 5.3 of the SmPC.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

2.3.2. Pharmacokinetics

In adults entecavir is rapidly absorbed from the gastrointestinal tract following oral administration with peak plasma concentration (C_{max}) occurring within 1 hour of drug administration. Administration of 0.5 mg entecavir with a standard high-fat meal (945 kcal, 54.6 g fat) or a light meal (379 kcal, 8.2 g fat) resulted in a minimal delay in absorption (1-1.5 hour fed vs. 0.75 hour fasted), a decrease in C_{max} of 44-46%, and a decrease in AUC of 18-20%. Renal excretion of unchanged drug is the primary route of elimination with biliary excretion playing a minor role. Entecavir terminal half-life (t½) in adults is approximately 140 hours, with an effective half-life for accumulation of approximately 24 hours.

The pharmacokinetics and pharmacodynamics of entecavir in pediatric patients was evaluated in two clinical studies AI463028 and AI463189.

The primary objective of study AI463028 was to determine the doses of ETV in children and adolescents that produce drug exposures comparable to those observed in adults given the 0.5 mg and 1.0 mg doses of ETV. The PK criteria were to achieve: 1) a median area under the concentration-time curve in one dosing interval, $AUC_{(TAU),}$ that was within ± 30% (13.1 - 24.3 ng•h/mL) of the median exposure (18.7 ng•h/mL) obtained from the adult Phase 2 PopPK analysis in nucleoside-naive subjects; and 2) a median $AUC_{(TAU)}$ in LVD-experienced subjects that was 37.4 ng•h/mL ± 30% (26.2 - 48.6 ng•h/mL). Safety, tolerability, and efficacy were secondary endpoints.

The target exposure was achieved in nucleoside-naive and LVD-experienced subjects, with ETV median $AUC_{(TAU)}$ ranging from 15.37 to 20.51 ng±h/mL and 32.33 to 43.91 ng/mL, respectively. Also, the target exposures in both populations were achieved across all 3 age groups, supporting the dosing recommendation for the Phase 3 efficacy and safety clinical study, AI463189.

The primary endpoint measure of study AI463189 (ongoing) was proportion of subjects achieving a composite of HBV DNA < 50 IU/mL and HBeAg seroconversion at Week 48. Children and adolescents 2 to < 18 years of age with CHB were enrolled in this study. Subjects were randomized 2:1 to ETV or placebo for a maximum of 96 weeks, with the primary endpoint at Week 48. The randomization was stratified by age group (2 to ≤ 6 years; > 6 to ≤ 12 years; > 12 to < 18 years).

A population pharmacokinetic (popPK) analysis was performed using data from studies AI463028 and AI463189 (n=121). In addition, PK data collected from adults (n=177) in previous clinical studies were included to enhance the model stability. A 2-compartment model with first-order absorption with allometric scaling of V and CL and an effect of age on the rate of absorption adequately described the data. The difference in the rate of absorption, which may be attributable to formulation rather than age, did not affect the relative bioavailablity. The model predicted exposure given the recommended dose

was 22% greater in pediatric patients aged 6 to <12 compared to adults, while more similar to adults in the other age groups as listed in Table 5.

Table 5. Simulation Results of Entecavir Mean AUCss(0-24) µg·h/L at Recommended Dose by Age Group

Age	10th	25th	50th	75th	90th
Adult	12.36	14.47	16.96	19.80	23.00
2 to < 6 yrs	13.25	15.55	18.18	20.93	24.15
6to < 12 yrs	14.24	17.54	20.72	22.32	25.83
12 to < 18 yrs	11.32	11.14	16.91	19.96	23.11

2.3.1. PK/PD modelling

The pharmacodynamics of entecavir in paediatric patients was explored using population pharmacodynamics (PopPD). The PopPD analysis utilized PD data collected in paediatric HBV patients between 2 and 18 years of age (Studies AI463028 and AI463189). In addition, PD data collected from adults were included to enhance the model stability. For all studies LVD-experienced subjects were excluded from the PopPD database. A total of 916 HBV DNA records were collected from 139 paediatric subjects (Studies AI463028 and AI463189) in the PopPD analysis dataset, and an additional 376 HBV DNA records from 110 adult subjects.

The PopPD analysis suggested that entecavir AUC increased the maximum change from baseline (RespMax) and decreased the time to half-maximal response (TDay50). The ALT normalized baseline viral load was shown to be predictive of RespMax, and RespMax was higher for subjects with a high baseline viral load; however, the probability of achieving a clinical response (HBV DNA < 50 IU/L) was lower. At the same baseline viral load, subjects with a high ALT had a greater likelihood of achieving a clinical response. Alanine aminotransferase was predictive of TDay50. Subjects with a high ALT took longer to achieve half-maximal response. There was no indication of a significant correlation between age and effect parameters (RespMax and TDay50).

2.3.2. Discussion and conclusion on clinical pharmacology

In the dose-finding study, AI463028, the target exposure was achieved across all 3 age groups, supporting the dosing recommendation for the Phase 3 efficacy and safety clinical study, AI463189.

The PopPK model adequately described the PK in paediatric patients. The mean model predicted exposure, given the recommended dose of 0.015 mg/kg up to a maximum dose of 0.5 mg under fasting conditions, was approximately 20% greater in pediatric patients aged 6 to <12 compared to adults, while the exposure was essentially the same as that in adults in the other age strata.

A food-interaction study conducted with the tablet formulation demonstrated a 20% reduction in area under the concentration-time curve when ETV was administered with a meal compared to ETV administered under fasting conditions. The results of this study led to the recommendation for the subsequent Phase 3 studies that ETV be administered on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal). Subsequent PPK and exposure-response analyses suggested that the modest decrease in ETV exposure when co-administered with a meal should not alter the

efficacy of ETV in the LVD-naïve adult population, but may result in suboptimal exposure in the LVD-refractory adult population. That conclusion resulted in the final recommendation in the SmPC that ETV can be administered without regards to food in the LVD-naïve adult population while maintaining the 2-hour window for LVD-refractory subjects. The global pediatric Phase 3 pediatric study, AI463189, was conducted with the 2-hour window for consistency with the most conservative labeling given that children are often considered a vulnerable population, particularly as any resistance risk could limit future treatment options. However, following comments from the rapporteurs regarding potential adherence issues associated with this recommendation the applicant evaluated the impact of concomitant food intake on the predicted exposure in pediatric patients. This simulation study suggested that the exposure will be adequate in most patients even with concomitant food intake. An altered dosing in the youngest patients (body weight <15.8) was proposed to accommodate dosing irrespective of food intake in all pediatric patients. Table 6 illustrates the final proposed dosing.

Table 6. Final paediatric dose to be administered once daily without regard to food

Body Weight (kg)	Body Weight (lbs)	Recommended Dose (mL)[a]
10.0 - 14.1	22.1 - 23.9	4.0
14.2 - 15.8	31.3 - 35.0	4.5
15.9 - 17.4	35.1 - 38.5	5.0
17.5 - 19.1	38.6 - 42.2	5.5
19.2 - 20.8	42.3 - 46.0	6.0
20.9 - 22.5	46.1 - 49.7	6.5
22.6 - 24.1	49.8 - 53.3	7.0
24.2 - 25.8	53.4 - 57.0	7.5
25.9 - 27.5	57.1 - 60.8	8.0
27.6 - 29.1	60.9 - 64.3	8.5
29.2 - 30.8	64.4 - 68.0	9.0
30.9 - 32.5	68.1 - 71.8	9.5
32.6 - 33.0	71.9 - 72.8	10.0

[a] Children with body weight ≥ 32.6 kg (71.9 lb) should receive 10.0 mL of oral solution or the 0.5 mg tablet.

There was no indication of a significant correlation between age and effect parameters, which supports the use of doses resulting in similar exposures in pediatric patients and adults.

In conclusion, the recommended dosing appears to result in exposures similar to those in adults across all paediatric age strata.

2.4. Clinical efficacy

The ETV paediatric development program is comprised of 2 ongoing studies. The first, Study AI463028 is a Phase 2b, single-arm, open-label study to assess the pharmacokinetics (PK), safety, tolerability, and preliminary efficacy of ETV in paediatric subjects with HBeAg-positive CHB. The second, Study AI463189, is a Phase 3 comparative, randomized, double-blind, placebo-controlled, multicenter study that compares the efficacy and safety of ETV with placebo in nucleoside-naive subjects with HBeAg-positive CHB.

The design of both paediatric studies includes long-term follow up for a total of 5 years (including on-treatment and post-study drug periods).

The subpopulation of patients with HBeAg+ infection was selected for paediatric study. This comprises the majority of paediatric patients and also has higher mean levels of plasma HBV-DNA than do the HBeAg- ones. Concerning treatment indications in paediatric, chronic HBV infection, see introduction to overview. Of note, the performed study had a virological endpoint and serves to validate the hypothesis of similar efficacy and safety as in adults, given similar drug exposure. Patients with HBeAg+ hepatitis have higher viral loads than those that are HBeAg-, and therefore, from a virological point of view, constitute the more “difficult to treat” side of the spectrum.

2.4.1. Dose finding study

AI463028 is an open-label study assessing the PK, safety, tolerability, and preliminary efficacy of ETV in paediatric subjects with HBeAg-positive chronic HBV (CHB) infection. Subjects are HBV-infected children and adolescents aged ≥ 2 - ≤ 18 years of age, enrolled into 1 of 3 age cohorts: Cohort 1 (≥ 2 - ≤ 6 years), Cohort 2 (> 6 - ≤ 12 years), and Cohort 3 (> 12 - ≤ 18 years of age).

A maximum of 64 evaluable subjects were to be enrolled into the 3 dose groups:

- Group A: 24 LVD-naive subjects at a starting dose of 0.015 mg/kg up to a maximum dose of 0.5 mg (8 subjects/cohort)
- Group B: 20 LVD-experienced subjects at a starting dose of 0.030 mg/kg up to a maximum of 1.0 mg (4 subjects in Cohort 1 and 8 subjects each in Cohorts 2 and 3). Accrual into each age cohort in Group B occurred when PK data from at least 4 subjects from Group A in the corresponding age cohort were evaluated by the MAH according to the protocol’s dose escalation rules.
- Group C: A maximum of 20 children who failed previous treatment with any non-ETV NA. Subjects were to be dosed at 0.030 mg/kg/day up to a maximum of 1.0 mg/day. Pharmacokinetic assessment was optional for Group C subjects.

The primary objective of this study was to find a paediatric dosing scheme for entecavir which would provide similar exposure as that seen in adults at the recommended dose, as discussed above. Virological endpoints were as follows:

Key Efficacy Endpoints on Treatment at Week 48 (NC = F) - Treated Subjects

Efficacy Endpoints	Number with Response/Number Evaluable (%) Group A LVD-naive N = 24	Group B LVD-exp N = 19
HBV DNA < 50 IU/ML	14/24 (58.3)	9/19 (47.4)
ALT NORMALIZATION (ALT <= 1.0 X ULN)	20/24 (83.3)	18/19 (94.7)
HBEAG SEROCONVERSION	10/24 (41.7)	3/19 (15.8)
PROTOCOL DEFINED RESPONSE (PDR)	7/24 (29.2)	3/19 (15.8)
MEAN LOG10 REDUCTION IN HBV DNA (IU/mL)*.....	- 5.86	- 5.36

PDR is defined as confirmed HBV DNA < 50 IU/mL plus confirmed HBeAg seroconversion on 2 sequential measurements at least 14 days apart.

* HBV DNA by COBAS TaqMan - HPS assay.

The point estimate for patients with HBV-DNA <50 IU/mL at 48 weeks in LVD naive patients is somewhat lower than in the pivotal adult study in a similar population (HbeAg+) (67%), whereas the HBeAg seroconversion rate was higher 42% versus 21% in the pivotal adult study.

Forty-seven percent (9/19) of LVD-experienced subjects in this study achieved HBV DNA < 50 IU/mL at Week 48, and 16% (3/19) achieved HBeAg seroconversion at this time point. By comparison, 19% and 8% of LVD-refractory adults achieved these respective efficacy endpoints at Week 48.Eleven of 13 Group B subjects (85%) treated through Week 96 achieved HBV DNA < 50 IU/mL at Week 96. This includes an additional 4 subjects compared to Week 48, and 7 of 10 Group B subjects with documented baseline LVDr.

In the pivotal LVD-refractory study in adults, the proportion of patients with HBV-DNA <50 IU/mL at week 48 was 19%, and the percentage of patients with HBeAg seroconversion was 8%. All in all, the pharmacokinetics, efficacy and safety outcomes of the AI463028 were supportive of further studies, and contribute to the evidence to substantiate the proposed paediatric indication. Notably, lamivudine resistance confers partial resistance to entecavir, as well as a broken barrier to resistance. For this reason, the adult dose in such patients is 1mg/day rather than 0.5 mg. Furthermore, the use of entecavir monotherapy in such patients is questionable, if other therapeutic alternatives are possible.

2.4.2. Main study

The main clinical outcomes study of this application is termed AI463189. This was a randomised, double blinded placebo controlled study of entecavir in HbeAg+ children.

Title of Study

Comparative Study of the Antiviral Efficacy and Safety of Entecavir (ETV) versus Placebo in Pediatric Subjects with Chronic Hepatitis B Virus (HBV) Infection who are HBeAg- Positive

Methods

Study participants

- Subjects were treated at 44 centres in this global study. Major inclusion criteria were as follows:

- a) History of CHB infection, defined as HBsAg-positive at the screening visit and on at least 1 other occasion ≥ 24 weeks prior to screening
- b) Detectable HBeAg AND no detectable anti-HBe antibodies at screening and at least once ≥4 weeks prior to screening
- c) Serum ALT 1.5 to < 10 x upper limit of normal (ULN) at screening and at least on 1 other occasion within 8 to 24 weeks prior to screening
- d) HBV DNA by polymerase chain reaction (PCR) ≥ 10^5 copies/mL at screening and evidence of the presence of HBV DNA at least once ≥4 weeks prior to screening
- Patients were males and females, 2 to < 18 years of age and could not have a history of more than 12 weeks of prior therapy with any nucleos(t)ide analogue with activity against hepatitis B.
- Major exclusion criteria included eGFR <50 mL/min/1.73m^2, co-infection with HIV, HCV or HDV, as well as past or present clinical hepatic decompensation or evidence of hepatic impairment (e.g. platelet count <70,000, S-bilirubin >2.5 mg/dL, INR >1.5, s-albumin <3.0 g/dL).

Treatments

For subjects taking ETV, it was dosed at 0.015 mg/kg/day up to a maximum dose of 0.5 mg/day using oral solution or tablets. A matching placebo was administered to the placebo subjects.

The dose selection for this study was based on pharmacokinetic (PK) data from Study AI463028. Study medication was to be taken on an empty stomach (2 hours before or 2 hours after food); therefore, it was suggested that subjects take their study medication at bedtime.

It is recognised that the treatment indication and therapeutic strategies in paediatric chronic HBV is not well defined. Furthermore, there is a non-negligible rate of spontaneous HBeAg seroconversion in paediatric patients. Along with advantages in defining the safety profile of the drug, this contributes to the rationale for a placebo controlled study. That said, it is noted that the study design and duration serves to confirm the hypothesis of relevant antiviral effects of entecavir, based on similar exposure as in the adults, rather than to define paediatric treatment strategies.

Objectives

Primary: To compare the proportion of subjects in each treatment group who achieve a combination of HBV deoxyribonucleic acid (DNA) suppression and hepatitis B e antigen (HBeAg) seroconversion (undetectable HBeAg AND detectable anti-HBe antibodies) at Week 48.

Secondary:

- Assess the serologic response rates (defined as hepatitis B surface antigen [HBsAg] loss and/or seroconversion; and HBeAg loss and/or seroconversion) including durability of response off treatment
- Assess the virological response rates
- Assess the biochemical response rates
- Assess ETV resistance rates
- Evaluate the long-term safety of ETV use in paediatric patients.

The objectives do not include an investigation of the appropriate treatment strategy in the target population, including a quantification of clinical benefit (reduction of progression to cirrhosis and hepatocellular carcinoma), which would require a large study of very long duration, but are considered reasonable given the expected scope of an antiviral efficacy and paediatric safety demonstration, given similar drug exposures as in an adult population.

Outcomes/endpoints

The primary endpoint was the proportion of subjects who achieved 1) HBV DNA < 50 IU/mL (approximately 300 copies/mL) using the Roche COBAS TaqMan HBV Test for use with the High Pure System (HPS) assay; and 2) HBeAg seroconversion (undetectable HBeAg AND detectable anti-HBe antibodies) at Week 48 of study treatment.

Key secondary endpoints included the following:

- Proportion of subjects with HBV DNA < 50 IU/mL at Week 48
- Proportion of subjects with serum ALT ≤ 1 X ULN at Week 48
- Proportion of subjects with HBV DNA < limit of quantitation (LOQ) (29 IU/mL) at Week 48
- Proportion of subjects with HBe seroconversion (undetectable HBeAg and presence of anti-HBe antibodies) at Week 48.

Safety endpoints were the number and percentage of subjects with AEs, serious adverse events (SAEs), discontinuations due to AEs, HBV disease progression, and laboratory abnormalities. Growth assessment (height and weight for age Z scores [HAZ and WAZ, respectively] and height and weight for age percentiles [HAP and WAP, respectively]) were also assessed.

Outcome measures are those generally used in studies of antivirals against CHB, and in trials of antivirals in paediatric patients.

Sample size

One hundred and twenty-three subjects (randomized 2:1 to ETV vs. placebo) in this study provided 90% power to show superiority of ETV vs. placebo assuming a response rate for the primary endpoint, HBV DNA by PCR < 50 IU/mL and HBeAg seroconversion, of 20% for ETV and 1% for placebo. A 2-sided significance level of 0.05 was used. Subjects who either discontinued from study treatment prior to Week 48 or had missing Week 48 HBV DNA or HBeAg serology measurement were considered as failures at Week 48 (non-completer = failure [NC = F]).

While the analysis of the primary endpoint was based on a randomized sample size of 123 subjects, the size of the overall study population was augmented to 180 randomized subjects in order to meet global regulatory requirements.

Randomisation

A randomized blocked design stratified by age group (2 to ≤6 years; > 6 to ≤ 12 years; > 12 to < 18 years) was used.

Blinding (masking)

The subject, investigator and BMS personnel involved in the conduct of the study were blinded to treatment assignment.

Statistical methods

Binary efficacy endpoints were analyzed using 2 algorithms:

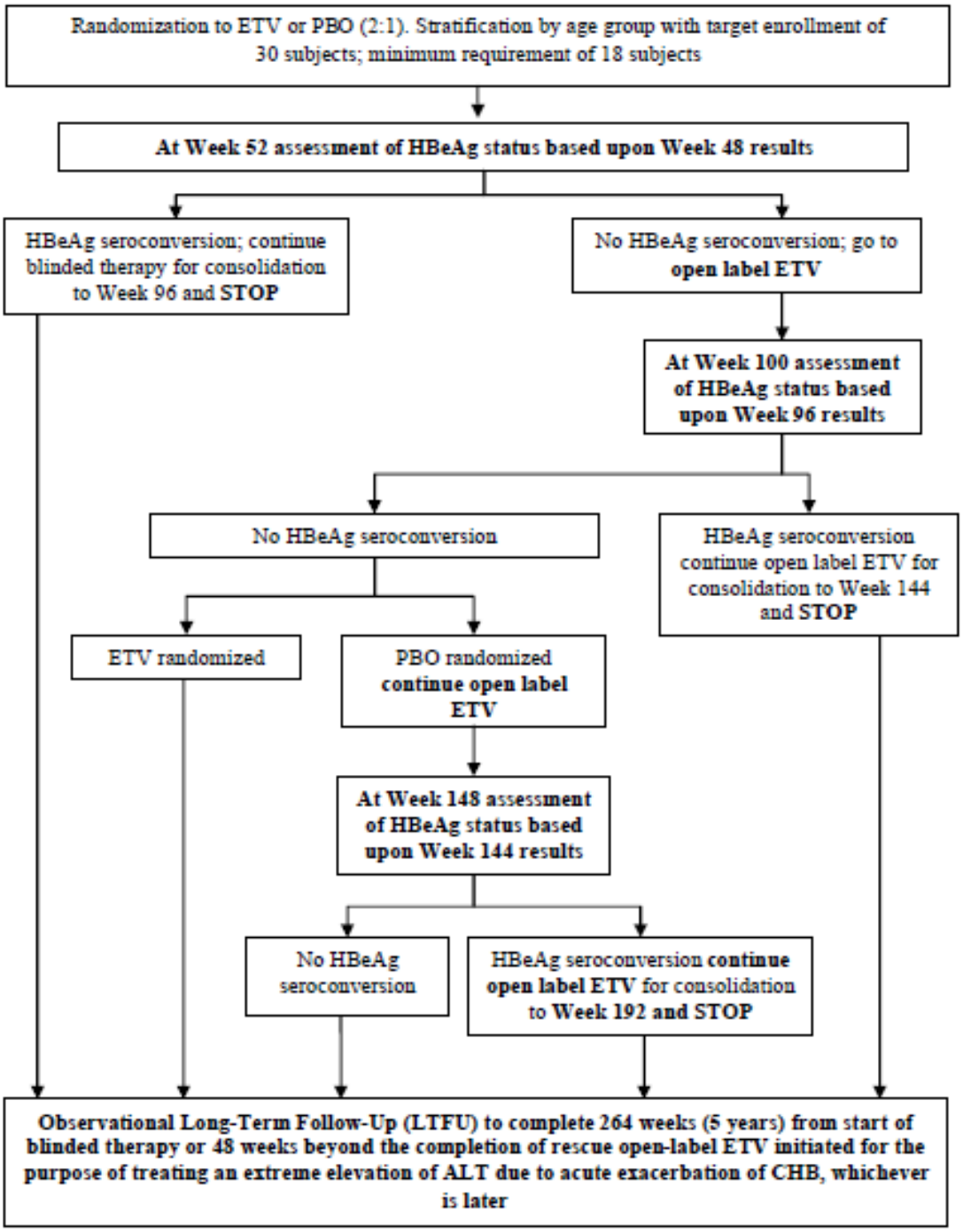
- NC = F: The numerator was based on subjects meeting the response criteria. The denominator was based on treated subjects. Subjects who had missing data at the analysis week were considered as failures.
- Non-completer = missing (NC = M): The numerator was based on subjects meeting the response criteria. The denominator was based on subjects with data at the analysis week. Subjects who had missing data at the analysis week were excluded.

Treatment regimens were compared using a difference in proportions (ETV - placebo), 95% confidence interval (CI) and p-value based on NC = F for the primary endpoint and key secondary endpoints. Analyses were stratified by age randomization strata. The proportions were computed within each stratum, and combined using a weighted average with weights proportional to stratum size (Cochran-Mantel-Haenszel weighting). Entecavir was considered superior to placebo if the p-value was < 0.05.

Results

Participant flow

AI463189 Study Schema



Overall, 228 subjects were enrolled. Of these subjects, 180 (79%) were randomized (120 and 60 in the ETV and placebo groups, respectively). Reasons for not being randomized were that the subject no longer met study criteria (43 subjects, with the majority due to screening ALT < inclusion threshold), subject withdrew consent (4 subjects), and other reason (1 subject had surgery to remove a possible malignant tumor). All 180 randomized subjects were treated.

There were 123 subjects in the primary cohort (82 and 41 in the ETV and placebo groups, respectively).

Subject disposition (start to end of treatment) Treated subjects

Status (%)	ETV N = 120	PBO N = 60	Total N = 180
TREATED	120 (100.0)	60 (100.0)	180 (100.0)
DISCONTINUED BEFORE WEEK 48	3 (2.5)	4 (6.7)	7 (3.9)
ADVERSE EVENT	0	2 (3.3)	2 (1.1)
SUBJECT WITHDREW CONSENT	3 (2.5)	1 (1.7)	4 (2.2)
PREGNANCY	0	1 (1.7)	1 (0.6)
DISCONTINUED AT WEEK 48 OR BEFORE WEEK 96	1 (0.8)	0	1 (0.6)
POOR/NON-COMPLIANCE	1 (0.8)	0	1 (0.6)
DISCONTINUED AT OR AFTER WEEK 96	0	0	0
COMPLETED TREATMENT	25 (20.8)	3 (5.0)	28 (15.6)
CONTINUING TREATMENT	91 (75.8)	53 (88.3)	144 (80.0)
ENTERED LONG-TERM FOLLOW-UP	14 (11.7)	6 (10.0)	20 (11.1)
DISCONTINUED LONG-TERM FOLLOW-UP	0	2 (3.3)	2 (1.1)
SUBJECT WITHDREW CONSENT	0	2 (3.3)	2 (1.1)
COMPLETED LONG-TERM FOLLOW-UP	0	0	0
CONTINUING LONG-TERM FOLLOW-UP	14 (11.7)	4 (6.7)	18 (10.0)
DID NOT ENTER LONG-TERM FOLLOW-UP	106 (88.3)	54 (90.0)	160 (88.9)

Baseline data

For the primary cohort, baseline demographics were consistent with the overall treated population demographics. The tables below present baseline demographics of the primary cohort, which comprises the subject of the primary efficacy analysis.

Demographics – primary cohort

	ETV N = 82	PBO N = 41	Total N = 123
AGE (YEARS)			
N	82	41	123
MEAN (SE)	10.1 (0.570)	10.5 (0.771)	10.2 (0.457)
SD	5.16	4.94	5.07
MEDIAN	10.0	11.0	11.0
MIN, MAX	2, 17	2, 17	2, 17
AGE RANDOMIZATION STRATA - N (%)			
>= 2 - <= 6 YRS	23 (28.0)	11 (26.8)	34 (27.6)
> 6 - <= 12 YRS	20 (24.4)	10 (24.4)	30 (24.4)
> 12 - < 18 YRS	39 (47.6)	20 (48.8)	59 (48.0)
GENDER - N (%)			
MALE	55 (67.1)	21 (51.2)	76 (61.8)
FEMALE	27 (32.9)	20 (48.8)	47 (38.2)
RACE - N (%)			
ASIAN	36 (43.9)	23 (56.1)	59 (48.0)
BLACK/AFRICAN AMERICAN	7 (8.5)	2 (4.9)	9 (7.3)
NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER	1 (1.2)	0	1 (0.8)
WHITE	36 (43.9)	15 (36.6)	51 (41.5)
OTHER	2 (2.4)	1 (2.4)	3 (2.4)
ETHNICITY - N (%)			
HISPANIC/LATINO	2 (2.4)	0	2 (1.6)
NOT HISPANIC/LATINO	33 (40.2)	14 (34.1)	47 (38.2)
NOT REPORTED	47 (57.3)	27 (65.9)	74 (60.2)

HBV characteristics – All Treated subjects

	ETV N = 120	PBO N = 60	Total N = 180
HBV DNA BY PCR (LOG10 IU/ML)			
N	120	60	180
MEAN (SE)	8.11 (0.0882)	7.96 (0.1308)	8.06 (0.0732)
SD	0.966	1.013	0.982
MEDIAN	8.29	8.00	8.17
MIN, MAX	4.9, 10.0	4.7, 9.7	4.7, 10.0
HBV DNA CATEGORY - N (%)			
< 8 LOG10 IU/ML	47 (39.2)	31 (51.7)	78 (43.3)
>= 8 LOG10 IU/ML	73 (60.8)	29 (48.3)	102 (56.7)
HEPATITIS B SURFACE ANTIGEN - N (%)			
POSITIVE	120 (100.0)	59 (98.3)	179 (99.4)
NEGATIVE	0	1 (1.7)	1 (0.6)
HEPATITIS B E ANTIGEN - N (%)			
POSITIVE	120 (100.0)	60 (100.0)	180 (100.0)
HEPATITIS B E ANTIBODY - N (%)			
POSITIVE	3 (2.5)	1 (1.7)	4 (2.2)
NEGATIVE	116 (96.7)	59 (98.3)	175 (97.2)
INDETERMINATE	1 (0.8)	0	1 (0.6)
HBV GENOTYPE - N (%)			
A	22 (18.3)	11 (18.3)	33 (18.3)
B	17 (14.2)	11 (18.3)	28 (15.6)
C	31 (25.8)	16 (26.7)	47 (26.1)
D	42 (35.0)	20 (33.3)	62 (34.4)
E	4 (3.3)	1 (1.7)	5 (2.8)
F	2 (1.7)	0	2 (1.1)
INDETERMINATE	2 (1.7)	1 (1.7)	3 (1.7)
INR			
N	120	60	180
MEAN (SE)	1.146 (0.01550)	1.068 (0.01656)	1.120 (0.01200)
MIN, MAX	0.88, 1.73	0.72, 1.52	0.72, 1.73
ALT (U/L)			
N	120	60	180
MEAN (SE)	107.1 (5.388)	94.4 (12.273)	102.8 (5.442)
MIN, MAX	28, 401	31, 764	28, 764
ALT CATEGORY* - N (%)			
<= 2 x ULN	23 (19.2)	17 (28.3)	40 (22.2)
>2 x ULN	97 (80.8)	43 (71.7)	140 (77.8)
> 2 - 5 X ULN	74 (61.7)	39 (65.0)	113 (62.8)
> 5 X ULN	23 (19.2)	4 (6.7)	27 (15.0)
ROUTE OF TRANSMISSION - N (%)			
MOTHER-TO-CHILD	70 (58.3)	29 (48.3)	99 (55.0)
HOUSEHOLD/CLOSE CONTACT	7 (5.8)	1 (1.7)	8 (4.4)
TRANSFUSION	7 (5.8)	4 (6.7)	11 (6.1)
UNKNOWN	36 (30.0)	26 (43.3)	62 (34.4)

In summary, this was a global study, where approximately half of the patients were treated at European centres, where genotypes A and D are dominant. There were somewhat more males in the entecavir arm, compared to the placebo group. Baseline HBV-DNA was somewhat higher in those randomised to entecavir.

Outcomes and estimation

Tests of primary and key secondary endpoints at week 48 – treated subjects – primary cohort

Endpoint	Number with Response/Number Evaluable (%) ETV N = 82	PBO N = 41	Difference in Prop. (ETV - PBO) (95% CI) [P-value]
PRIMARY: HBV DNA < 50 IU/ML AND HBEAG SEROCONVERSION AT WEEK 48	20/82 (24.4)	1/41 (2.4)	20.2 (9.1, 31.4) [0.0049]
KEY SECONDARY:			
HBV DNA < 50 IU/ML AT WEEK 48	38/82 (46.3)	1/41 (2.4)	41.8 (29.4, 54.2) [<0.0001]
ALT NORMALIZATION AT WEEK 48	55/82 (67.1)	9/41 (22.0)	45.2 (29.2, 61.2) [<0.0001]
HBV DNA < LOQ AT WEEK 48	35/82 (42.7)	1/41 (2.4)	38.2 (25.9, 50.5) [<0.0001]
HBEAG SEROCONVERSION AT WEEK 48	20/82 (24.4)	5/41 (12.2)	12.1 (-1.5, 25.7) [0.11]

The proportion of patients withHBeAg seroconversion, representing the primary virological goal of treatment in an HBeAg+ population, at week 48 was 24.4% in the entecavir group and 12.2% in the placebo group. This finding is of borderline statistical significance. Other available data and its covariance with virological suppression (see subgroup analysis below) supports that the difference is real.

Whereas only one patient in the placebo group reached the virological endpoint of HBV-DNA <50 IU/mL, this endpoint was reached by 46% in the entecavir group. The latter figure is lower than in the pivotal HBeAg+ study in adults (67%). Concerning virological breakthroughs and resistance, see below.

As drug exposure at the given dose is anticipated to have been similar in children and adults, this factor does not likely contribute to the differences in response between children and adults.

Compared to the comparable adult trial population, the children had lower HBV-DNA on average, whereas response is generally higher in patients with lower HBV-DNA. Conversely, responses are higher with higher baseline ALT. When comparing adult and paediatric response per ALT stratum, responses were higher in adults across ALT level strata. it is notable that experience from HIV indicates that virological outcomes with chronic antiviral therapy is often lower in children than in adults despite doses expected to yield similar exposure, perhaps due to differences in adherence. Available measurements from the present study, however, are not indicative of low adherence.

The results from the pivotal paediatric trial are solidly in support of a considerable antiviral effect over placebo.

HBV DNA Values and Changes from Baseline - On Treatment through Week 48 - Treated Subjects - Primary Cohort

		HBV DNA (log10 IU/mL)												
						Percentiles				Change from Baseline				
Timepoint	Treatment Group	N#	Mean	SD	Min	25	Median	75	Max	N#	Mean	SE	Median	IQR
BASELINE	ETV	82	8.06	1.015	4.9	7.64	8.17	8.63	10.0					
	PBO	41	7.83	0.896	5.6	7.52	7.96	8.51	9.2					
WEEK 4	ETV	78	5.18	1.077	2.6	4.53	5.00	5.74	7.7	78	-2.90	0.1056	-3.14	1.08
	PBO	40	7.79	0.990	4.4	7.43	7.91	8.32	9.6	40	-0.01	0.0667	-0.01	0.30
WEEK 12	ETV	77	3.96	1.286	1.4	3.01	4.05	4.74	7.6	77	-4.09	0.1273	-4.24	1.04
	PBO	39	7.55	1.376	3.2	7.17	7.93	8.41	9.4	39	-0.31	0.1319	-0.03	0.51
WEEK 24	ETV	75	3.06	1.417	1.4	1.70	2.78	4.18	7.7	75	-4.98	0.1364	-5.06	1.64
	PBO	38	7.51	1.354	2.3	6.90	7.80	8.54	9.1	38	-0.37	0.1228	-0.15	0.50
WEEK 36	ETV	70	2.55	1.269	1.4	1.45	1.81	3.76	5.4	70	-5.53	0.1129	-5.58	1.45
	PBO	36	7.20	1.941	1.4	6.88	7.75	8.55	9.8	36	-0.76	0.2685	-0.14	1.37
WEEK 48	ETV	80	2.48	1.266	1.4	1.45	1.85	3.60	7.8	80	-5.57	0.1307	-5.84	1.35
	PBO	37	7.04	1.948	1.4	6.77	7.54	8.36	9.2	37	-0.85	0.2573	-0.14	1.56

number of subjects with baseline and timepoint results

Mean decrease of HBV-DNA from baseline at week 48 was 5.57 $\log_{10}$. The mean decrease over placebo was 4.70. In the AI463022 (pivotal nucleoside naive HBeAg+ study in adults), the median decrease from baseline at 48 weeks was 6.78 $\log_{10}$.

Additional Efficacy Endpoints (NC = F) - On Treatment at Week 48 - Treated Subjects - Primary Cohort

	Number with Response/Number Evaluable (%)	
	ETV N=82	PBO N=41
HBV DNA < 50 IU/mL and ALT Normalization	32/82 (39.0)	1/41 (2.4)
HBV < LLD (10 IU/mL)	5/82 (6.1)	0/41
HBV DNA Categories		
< LOQ (29 IU/mL)	35/82 (42.7)	1/41 (2.4)
LOQ - < 50 IU/mL	3/82 (3.7)	0/41
50 - < 172 IU/mL	7/82 (8.5)	0/41
172 - < 1,720 IU/mL	11/82 (13.4)	2/41 (4.9)
1,720 - < 17, 200 IU/mL	16/82 (19.5)	1/41 (2.4)
>= 17, 2000 IU/mL	8/82 (9.8)	33/41 (80.5)
NOT REPORTED	2/82 (2.4)	4/41 (9.8)
HBeAg Loss	21/82 (25.6)	5/41 (12.2)
HBsAg Loss	2/82 (2.4)	1/41 (2.4)
HBsAg Seroconversion	1/82 (1.2)	0/41

As expected, HBsAg loss and seroconverison rates were low.

Subgroup analyses of efficacy

Plasma HBV-DNA <50 copies/mL

HBV DNA < 50 IU/mL (NC = F and NC = M) by Subgroups - On Treatment at Week 48 - Treated Subjects - Primary Cohort

Analysis Method Subgroup Level	Number with Response/Number Evaluable (%) ETV N=82	 PBO N=41
NC = F		
RANDOMIZATION AGE STRATUM		
>= 2 - <= 6 YRS	10/23 (43.5)	1/11 (9.1)
> 6 - <= 12 YRS	9/20 (45.0)	0/10
> 12 - < 18 YRS	19/39 (48.7)	0/20
GENDER		
MALE	26/55 (47.3)	0/21
FEMALE	12/27 (44.4)	1/20 (5.0)
BASELINE HBV DNA		
< 8 LOG10 IU/ML	26/34 (76.5)	1/23 (4.3)
>= 8 LOG10 IU/ML	12/48 (25.0)	0/18
BASELINE ALT		
<= 2 X ULN	3/14 (21.4)	1/11 (9.1)
> 2 X ULN	35/68 (51.5)	0/30
> 2 - 5 X ULN	26/52 (50.0)	0/27
> 5 X ULN	9/16 (56.3)	0/3
REGION		
ASIA	12/16 (75.0)	0/11
EUROPE	11/36 (30.6)	1/21 (4.8)
NORTH/SOUTH AMERICA	15/30 (50.0)	0/9
NC = F		
GENOTYPE		
A	11/15 (73.3)	0/8
B	4/7 (57.1)	0/7
C	15/23 (65.2)	0/14
D	5/31 (16.1)	1/10 (10.0)
OTHER	3/6 (50.0)	0/2
ROUTE OF TRANSMISSION		
MOTHER-TO-CHILD	27/50 (54.0)	1/22 (4.5)
HOUSEHOLD/CLOSE CONTACT	3/6 (50.0)	0/1
TRANSFUSION	1/5 (20.0)	0/3
UNKNOWN	7/21 (33.3)	0/15

Baseline HBV-DNA is a known predictor of the likelihood of achieving HBV-DNA <50 IU/mL, as is baseline ALT. The lack of a difference in response over age cohorts is reassuring in terms of the appropriateness of the selected dosing regimen.

In the ETV group at Week 48 (NC = F), although the sample sizes were small, a numerically lower proportion of subjects with Genotype D achieved HBV DNA < 50 IU/mL (5/31 subjects [16%]) than subjects with other genotypes (11/15 subjects [73%], 4/7 subjects [57%], 15/23 subjects [65%], and

3/6 subjects [50%] in subjects with Genotypes A, B, C, and other [E, F, or indeterminate, respectively).

As a corollary, a numerically lower proportion of subjects in Europe achieved HBV DNA < 50 IU/mL (11/36 subjects [31%]) compared to ETV subjects from Asia (12/16 subjects [75%]) or North/South America (15/30 subjects [50%]).

In the ETV group of the primary cohort, there was notable overlap between subjects with high baseline HBV DNA (≥ 8 log10 IU/mL) and those with Genotype D disease (52%; 25/48 ETV subjects with high baseline DNA); this correlation was not present among placebo subjects. The majority of Genotype D subjects in the ETV group were from European sites (52%; 25/48 ETV subjects with Genotype D were from Europe).

Of note, the in vitro antiviral efficacy of entecavir (EC_{50}) is similar across genotypes. Furthermore, the MAH has provided a systematic review of outcomes by genotype in the adult program. This does not indicate lower response rates in genotype D. The barrier to resistance of entecavir appeared similarly high regardless of viral genotype (see below). Also, the higher baseline viral loads that correlate with genotype D in the AI463189 study are not a general phenomenon. On this basis, it is concluded that the lower efficacy seen in genotype D in the AI463189 study, is likely an effect of a small sample and confounded by higher baseline viral loads.

HBeAg seroconversion

HBeAg seroconversion (NC= F and NC=M) by subgroups – on treatment at week 48 – treated subjects – primary cohort

Analysis Method Subgroup Level	Number with Response/Number Evaluable (%) ETV N=82	 PBO N=41
NC = F		
RANDOMIZATION AGE STRATUM		
>= 2 - <= 6 YRS	7/23 (30.4)	2/11 (18.2)
> 6 - <= 12 YRS	5/20 (25.0)	1/10 (10.0)
> 12 - < 18 YRS	8/39 (20.5)	2/20 (10.0)
GENDER		
MALE	14/55 (25.5)	2/21 (9.5)
FEMALE	6/27 (22.2)	3/20 (15.0)
BASELINE HBV DNA		
< 8 LOG10 IU/ML	15/34 (44.1)	5/23 (21.7)
>= 8 LOG10 IU/ML	5/48 (10.4)	0/18
BASELINE ALT		
<= 2 X ULN	2/14 (14.3)	2/11 (18.2)
> 2 X ULN	18/68 (26.5)	3/30 (10.0)
> 2 - 5 X ULN	12/52 (23.1)	3/27 (11.1)
> 5 X ULN	6/16 (37.5)	0/3
REGION		
ASIA	5/16 (31.3)	1/11 (9.1)
EUROPE	6/36 (16.7)	4/21 (19.0)
NORTH/SOUTH AMERICA	9/30 (30.0)	0/9
NC = F		
GENOTYPE		
A	6/15 (40.0)	1/8 (12.5)
B	1/7 (14.3)	0/7
C	8/23 (34.8)	1/14 (7.1)
D	3/31 (9.7)	3/10 (30.0)
OTHER	2/6 (33.3)	0/2
ROUTE OF TRANSMISSION		
MOTHER-TO-CHILD	13/50 (26.0)	4/22 (18.2)
HOUSEHOLD/CLOSE CONTACT	3/6 (50.0)	0/1
TRANSFUSION	1/5 (20.0)	0/3
UNKNOWN	3/21 (14.3)	1/15 (6.7)

At Week 48 (NC = F) in the ETV group, subjects with HBV Genotypes A and C had the highest rates of HBeAg seroconversion (6/15 subjects [40%] and 8/23 subjects [35%], respectively). Genotype D subjects had the lowest rates of HBeAg seroconversion at Week 48 (3/31 subjects [10%]). In the placebo group, 3 of 10 subjects (30%) with Genotype D achieved HBeAg seroconversion, and 1 of 14 subjects (7%) with Genotype C achieved this endpoint. No subjects in the placebo group with Genotype B (0/7) or other (0/2 with E, F, or indeterminate) achieved HBeAg seroconversion at Week 48.

These differential results correlate with the findings on HBV-DNA (see above). They should be interpreted with caution due to the small sample size, and the non-random distribution of different genotypes, e.g., across regions. The higher seroconversion rates seen for entecavir in the lowest age group correlate with findings from the placebo group.

Virological response and emerging drug resistance

Virological breakthroughs

There were 2 nucleoside-naïve subjects with virologic breakthrough (defined as ≥1 log10 HBV DNA increase over nadir) in Year 1 from the Integrated Naïve Primary Resistance Cohort, 1 subject each from AI463028 and AI463189. In Year 2, there were 3 breakthroughs from Study AI463028, including one with a prior breakthrough in Year 1. Thus, there was a total of 4 subjects with virologic breakthrough through Years 1 and 2 in the Integrated Naïve Primary Resistance Cohort.

No ETV-treated LVD-experienced subjects experienced a virologic breakthrough in Year 1.

Viral drug resistance

In Year 1, there were 115 subjects in the Integrated Naive Primary Resistance Cohort with an on-treatment HBV DNA result, and 110 of them had an HBV DNA sample available for resistance testing (i.e., *treated and monitored group*). Ninety-three of 110 treated and monitored subjects had baseline samples available for genotypic analysis. Neither ETVr nor LVDr substitutions were detected at baseline in 91 samples successfully analyzed. One subject had an adefovir-resistance (ADVr) mutation (A181A/T) at baseline; however, this substitution was not detected at later time points during the study. During Year 1, no subject developed ETVr, LVDr, or ADVr substitutions during treatment with ETV. Therefore, through Year 1, the cumulative probability of genotypic ETVr was zero.

The naive cohort from AI463028 has full resistance observations available through Week 96; 1 subject was observed to have emergent LVDr HBV at the Week 96 visit, having had no evidence for LVDr at Week 48 (this subject had no baseline sample available for genotypic testing).

Among LVD-experienced children in Study AI463028, there was 1 subject who had on-treatment ETVr at both Weeks 48 and 96, but there was no available baseline sample to distinguish whether this resistance was acquired prior to or during ETV use

In adults, the probability of treatment emergent ETV resistance in patients without prior LVD experience (and resistance) over 5 years was 1.2%. In patients with prior LVD resistance, which also confers partial resistance to ETV, the probability of ETV resistance over 5 years was approximately 50%. Available data are not indicative of a different resistance profile when paediatric patients are treated. Of note, viral breakthrough in the absence of emerging drug resistance may be indicative of lapsing adherence to treatment.

Overall cohort and longer term follow up

During the review period, the MAH provided supplementary data on 48 weeks outcomes in the overall cohort, as well as 96 weeks data in the primary cohort. These are supportive of conclusion drawn on the basis of 48 week data. Notably, as anticipated, the proportion of virological responders increased from week 48 to week 96, particularly among those with high baseline HBV-DNA.

Summary of Efficacy Endpoints at Week 48 (NC = F) in Study AI463189

Endpoint	Overall Cohort (N=180)		Primary Cohort (N=123)	
	ETV (N=120) % (Responder/Evaluable)	Placebo (N=60) % (Responder/Evaluable)	ETV (N=82) % (Responder/Evaluable)	Placebo (N=41) % (Responder/Evaluable)
HVB DNA < 50 IU/mL and HBeAg Seroconversion	24 (29/120)	3 (2/60)	24 (20/82)	2 (1/41)
HBV DNA < 50 IU/mL	49 (59/120)	3 (2/60)	46 (38/82)	2 (1/41)
ALT Normalization	68 (81/120)	23 (14/60)	67 (55/82)	22 (9/41)
HBV DNA < LOQ	47 (56/120)	3 (2/60)	43 (35/82)	2 (1/.41)
HBeAg Seroconversion	24(29/120)	10 (6/60)	24 (20/82)	12 (5/41)

Summary of Efficacy Results for Primary Cohort (NC = F) in Study AI463189

Endpoint	ETV (N=82) % (Responder/Evaluable)	
	Week 48	Week 96
HVB DNA < 50 IU/mL and HBeAg Seroconversion	24 (20/82)	35 (29/82)
HBV DNA <50 IU/mL	46 (38/82)	61 (50/82)
< 8 log10 IU/mL	77 (26/34)	79 (27/34)
≥ 8 log10 IU/mL	25 (12/48)	48 (23/48)
Genotype		
A	73 (11/15)	73 (11/15)
B	57 (4/7)	71 (5/7)
C	65 (15/23)	78 (18/23)
D	16 (5/31)	39 (12/31)
Other	50 (3/6)	67 (4/6)
ALT Normalization	67 (55/82)	83 (68/82)
HBeAg seroconversion	24 (20/82)	35 (29/82)

Summary of Efficacy for trial AI463189

A Comparative Study of the Antiviral Efficacy and Safety of Entecavir (ETV) versus Placebo in Pediatric Subjects with Chronic Hepatitis B Virus (HBV) Infection who are HBeAg-Positive			
Study identifier	A463189		
Design	Randomised, double blind, placebo controlled study of entecavir in HBeAg+ children		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	48 weeks not applicable 216 weeks (total study duration 264 weeks)	
Hypothesis	Superiority		
Treatment groups	Entecavir 0.015 mg/kg/day	N=120	
	Placebo	N=60	
Endpoints and definitions	Primary endpoint	The proportion of subjects that achieved plasma HBV-DNA <50 IU/mL and HBeAg seroconversion	
	Secondary endpoint	The proportion of subjects that achieved plasma HBV-DNA <50 IU/mL	
	Secondary endpoint	The proportion of subjects that achieved HBeAg seroconversion	
Database lock	12 April 2013		
Results and analysis			
Analysis description	**Primary analysis**		
Analysis population and time point description	Intent to treat at 48 weeks of therapy		
Descriptive statistics	Treatment group	Entecavir	Placebo
	Number of subjects	82	41
	Proportion of subjects that achieved plasma HBV-DNA <50 IU/mL and HBeAg seroconversion (%)	24.4	2.4
	Proportion of subjects that achieved plasma HBV-DNA <50 IU/mL (%)	46.3	2.4
	The proportion of subjects that achieved HBeAg seroconversion	24.4	12.2.
Effect estimate per comparison	Proportion of subjects that achieved plasma HBV-DNA <50 IU/mL and HBeAg seroconversion (%)	Comparison groups	Entecavir versus placebo
		Difference in proportions	20.2
		95% CI	9.1-31.4
		P-value	0.0049
	Proportion of subjects that achieved plasma HBV-DNA <50 IU/mL (%)	Comparison groups	Entecavir versus placebo
		Difference in proportions	41.8
		95% CI	29.4-54.2
		P-value	<0.0001
	The proportion of subjects that achieved HBeAg seroconversion	Comparison groups	Entecavir versus placebo
		Difference in proportions	12.1
		95% CI	-1.5-25.7
		P-value	0.11

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant has performed one PK study in nucleoside naive and –experienced patients, and subsequently one pivotal, placebo controlled study in nucleoside naive patients with HBeAg+ CHB. In general, paediatric indications for antivirals have been based on PK data showing that a selected dosing regimen yields comparable drug exposure as in adults, in combination with a larger efficacy and safety study (often without a control group) to corroborate assumptions of efficacy and safety, and to investigate paediatric specific safety concerns, such as impact on growth and development. The use of a placebo group in this case is appropriate as there is spontaneous HBeAg seroconversion and the natural course of HBV in children needs to be accounted for.

The studies performed by the applicant are in line with this paradigm and are therefore inherently sufficient to evaluate the paediatric use of entecavir. It is recognised that the studies investigate the antiviral efficacy and not primarily the clinical benefit of entecavir use in children. It is generally recognised that strategic studies to define the appropriate use and the long term benefits of antiviral therapy against CHB in children are needed (see e.g., Sokal et al, J Hepatol 2013). However, such studies would need to be rather large and long term, and could hardly be expected as a basis for a paediatric indication.

Efficacy data and additional analyses

Available PK data indicate comparative drug exposure between adults and children over the relevant age range. Efficacy data, mainly in nucleoside naive HBeAg+ children indicate an antiviral efficacy that is considerably greater than seen with placebo, including higher levels of HBeAg seroconversion, a finding of borderline statistical significance. The absolute antiviral efficacy in terms of impact on viral replication is lower than seen in a comparative adult population. In particular, results were poor in patients with genotype D infection, mostly prevalent in Europe. The MAH has thoroughly discussed this issue; in vitro susceptibility to genotype D is similar to other genotypes, and there is no external support from other studies of entecavir to support a differential efficacy depending on genotype. While baseline HBV-DNA is higher in patients with genotype D in the AI463189 study, this is not a general finding. To the extent that the relatively low responses in genotype D in the small sample of this study can be understood, the higher baseline HBV-DNA in these patients seems the most likely explanation.

It is reassuring that available data do not indicate higher levels of development of drug resistance in nucleoside naive patients than was seen in adult patients. Therefore, it may be that adherence to therapy plays a role, although this is not evident based on on-treatment measurements. The sparse available data on the treatment of lamivudine experienced patients show better point estimates for virological efficacy compared to adults. However, there are no reasons to believe that the limitations of efficacy and durability of response due to a limited barrier to resistance for entecavir would not be relevant for children with hepatitis B.

2.4.4. Conclusions on the clinical efficacy

The applicant has demonstrated comparative PK as in adults, and antiviral efficacy that clearly exceeds placebo, though apparently lower than in a comparative adult population. Furthermore, similar to the adult population, a high barrier to resistance has been shown in nucleoside naive patients, indicating that the antiviral effect may be anticipated to be durable.

2.5. Clinical safety

2.5.1. Introduction

In clinical studies in adult patients with compensated liver disease, the most common adverse reactions of any severity with at least a possible relation to entecavir were headache (9%), fatigue (6%), dizziness (4%) and nausea (3%). Exacerbations of hepatitis during and after discontinuation of entecavir therapy have also been reported.

Patient exposure

Safety data from 2 paediatric studies, AI463028 and AI463189, were provided in this application. All subjects in Study AI463189 are LVD-naive, and have been treated with ETV or placebo or placebo subjects crossing over to open-label ETV for Year 2. In Study AI463028, subjects in group A are LVD-naive, subjects in Group B are LVD experienced, and subjects in Group C are NA experienced.

Time on ETV or Placebo and in Follow Up - Nucleoside-naive Subjects

							Percentiles			
Weeks	Treatment Group	N	Mean	SD	SE	Min	25	Median	75	Max
TIME ON THERAPY (WEEKS)										
	Integrated Naive Safety Cohort	173	61.1	32.87	2.499	2.4	35.3	60.3	95.9	121.6
	PBO	60	43.5	20.18	2.606	1.1	35.7	50.4	52.1	98.9
TIME ON STUDY SINCE STARTING ETV										
	Integrated Naive Safety Cohort	173	83.4	70.27	5.343	4.0	36.1	61.0	101.4	270.1
TIME IN OFF-TREATMENT FOLLOW-UP										
	Integrated Naive Safety Cohort	29	88.9	76.02	14.116	5.3	23.3	42.0	168.3	204.4
	PBO	4	16.8	4.75	2.377	12.4	13.2	15.8	20.4	23.1
TIME IN LONG-TERM FOLLOW-UP										
	Integrated Naive Safety Cohort	36	101.4	73.39	12.232	5.4	24.1	127.6	168.4	204.6
	PBO	6	20.1	15.44	6.305	4.4	12.4	15.8	23.1	49.0

Time on ETV or Placebo and in Follow Up - Nucleoside-experienced Subjects

							Percentiles			
Weeks	Treatment Group	N	Mean	SD	SE	Min	25	Median	75	Max
TIME ON ETV										
	Integrated Experienced Safety Cohort	24	81.3	27.27	5.567	24.0	61.3	96.2	101.9	122.3
TIME ON STUDY SINCE STARTING ETV										
	Integrated Experienced Safety Cohort	24	159.7	72.75	14.850	24.1	96.3	192.6	216.9	236.7
TIME IN OFF-TREATMENT FOLLOW-UP										
	Integrated Experienced Safety Cohort	12	93.9	48.78	14.082	24.1	54.0	92.8	129.5	182.6
TIME IN LONG-TERM FOLLOW-UP										
	Integrated Experienced Safety Cohort	18	104.2	36.59	8.623	24.3	84.1	110.6	120.1	182.7

Overall exposure amounts to 173 paediatric patients treated with entecavir for a median of 60 weeks in the nucleoside naive cohort and 24 paediatric patients treated with entecavir for a median of 96 weeks in the nucleoside experienced cohort. The maximal duration of treatment with entecavir under the present protocol is stated to be 122 weeks.

Adverse events

In the placebo-controlled AI463189 study adverse events were as follows:

Summary of Adverse Events and Select and Select Laboratory Abnormalities Through Week 48 – Treated Subjects

	No. of Subjects (%)	
Event	**ETV (N = 120)**	**Placebo (N = 60)**
Deaths*	0	0
Serious Adverse Events	4 (3.3)	7 (11.7)
Discontinuations Due to Adverse Events	0	2 (3.3)
Any Adverse Event	74 (61.7)	43 (71.7)
Most Common Adverse Events (≥ 10% of Subjects in Either Group)		
Upper Respiratory Tract Infection	15 (12.5)	6 (10.0)
Nasopharyngitis	11 (9.2)	7 (11.7)
Pyrexia	11 (9.2)	7 (11.7)
Vomiting	9 (7.5)	8 (13.3)
Cough	8 (6.7)	6 (10.0)
Diarrhea	3 (2.5)	6 (10.0)
Related Adverse Events	10 (8.3)	6 (10.0)
Related Grade 2 - 4 Adverse Events	4 (3.3)	2 (3.3)
Grade 3 - 4 Adverse Events	4 (3.3)	3 (5.0)
Malignancies	0	0
ALT Flares	2 (1.7)	5 (8.3)
Hepatic Disease Progression	0	0

Similar to what has been seen in the adult studies, there is no clearly apparent outstanding side effects profile of entecavir when compared to placebo.

Serious adverse event / deaths / other significant events

No deaths were reported. Six subjects (4%) in the integrated naive safety cohort had SAEs. These included hydrocele, chronic otitis media, tonsillar hypertrophy, asthma exacerbation, ALT flare, pneumonia and gastroenteritis. None of the subjects in the integrated experienced safety cohort had SAEs. No apparent pattern emerges in the SAE narratives of patients treated with entecavir.

Laboratory findings

Haematology

Nucleoside-naive Subjects

In the integrated naive safety cohort, the rates of Grade 1 - 4 hemoglobin, platelets, INR, and WBC were 1% - 6%. Eleven percent of subjects had Grade 1 - 4 ANCs. One subject had a Grade 3 - 4 ANC.

In the placebo group, 7% of subjects had Grade 1 - 4 hemoglobin and 10% of subjects had Grade 1 - 4 INR. All other Grade 1 - 4 hematologic abnormalities were reported in 2% - 3% of subjects. One subject each had Grade 3 - 4 INR and ANC.

Nucleoside-experienced Subjects

In the integrated experienced safety cohort, 3 subjects (13%) each had Grade 1 - 4 INR and ANCs and 1 subject had Grade 1 - 4 haemoglobin. One subject had a Grade 3 - 4 ANC.

Of note, entecavir has not been associated with any haematological side effects in the adult population.

Liver function

Nucleoside-naive Subjects

The rates of Grade 1 - 4 ALT were comparable between the integrated naive safety cohort and the placebo group (92% vs. 98%) while the rates of Grade 1-4 AST were lower in the integrated safety cohort compared to the placebo group (68% vs. 85%). The rates of Grade 3 - 4 ALT and AST were comparable between the integrated naive safety cohort and placebo group (24% and 4% vs. 30% and 8%, respectively).

Nucleoside-experienced Subjects

In the integrated experienced safety cohort, 88% of subjects had Grade 1 - 4 ALT and 42% of subjects had Grade 1 - 4 AST. Three subjects (13%) had Grade 3 - 4 ALT.

Select Laboratory Elevations and Abnormalities – Nucleoside-naïve Subjects-Treated Subjects

Number with Elevations or Abnormalities/ Number with Measurements (%)	Integrated Naive Safety Cohort N = 173		PBO N = 60	
ANY GRADE 3-4 LABORATORY ABNORMALITY	45/171	(26.3)	19/60	(31.7)
ALT > 2 X B/L & > 10 X ULN (ALT FLARE)	5/171	(2.9)	5/60	(8.3)
SIMULTANEOUS ALT > 2 X B/L & TBILI > 2 X B/L & > 2 X ULN	0/171		1/60	(1.7)
ALBUMIN < 2.5 G/DL	0/171		0/60	
CONFIRMED CREATININE INCREASE FROM B/L >= 0.3 MG/DL	2/171	(1.2)	0/60	
CONFIRMED CREATININE INCREASE FROM B/L >= 0.5 MG/DL	0/171		0/60	

Select Laboratory Elevations and Abnormalities – Nucleoside-experienced Subjects

Number with Elevations or Abnormalities/ Number with Measurements (%)	Integrated Experienced safety Cohort N = 24
ANY GRADE 3-4 LABORATORY ABNORMALITY	4/ 24 (16.7)
ALT > 2 X B/L & > 10 X ULN (ALT FLARE)	0/ 24
SIMULTANEOUS ALT > 2 X B/L & TBILI > 2 X B/L & > 2 X ULN	0/ 24
ALBUMIN < 2.5 G/DL	0/ 24
CONFIRMED CREATININE INCREASE FROM B/L >= 0.3 MG/DL	0/ 24
CONFIRMED CREATININE INCREASE FROM B/L >= 0.5 MG/DL	0/ 24

Growth assessment

On Treatment Growth Assessment and Changes from Baseline – Treated Subjects

						Percentiles		Change from Baseline			
Timepoint	Treatment Group	N#	Mean	SD	Min	Median	Max	N#	Mean	SE	Median
					Height For Age Percentile						
BASELINE	ETV	120	49.07	28.996	0.0	48.99	99.6				
	PBO	60	53.21	25.613	0.2	50.62	99.5				
WEEK 24	ETV	101	49.42	29.079	0.2	49.51	99.7	101	-0.72	0.6052	-0.37
	PBO	52	52.15	26.397	0.2	48.98	99.5	52	-0.78	1.1386	0.05
WEEK 48	ETV	85	50.18	29.506	1.7	49.21	99.7	85	-1.41	0.8355	-1.12
	PBO	41	53.06	24.340	0.2	52.50	99.2	41	-0.52	1.5544	0.04
WEEK 96	ETV	37	53.20	31.306	5.5	62.42	92.5	37	1.52	1.7023	0.61
	PBO	14	50.56	27.684	0.4	41.84	97.3	14	2.60	3.6315	-0.19
					Height For Age Z Score						
BASELINE	ETV	120	-0.07	1.200	-6.9	-0.03	2.7				
	PBO	60	0.10	0.918	-2.9	0.02	2.6				
WEEK 24	ETV	101	-0.01	1.042	-2.9	-0.01	2.8	101	-0.02	0.0211	-0.02
	PBO	52	0.08	0.952	-2.8	-0.03	2.6	52	-0.01	0.0335	0.01
WEEK 48	ETV	85	0.02	0.991	-2.1	-0.02	2.8	85	-0.04	0.0293	-0.05
	PBO	41	0.10	0.875	-2.8	0.06	2.4	41	-0.00	0.0491	0.00
WEEK 96	ETV	37	0.08	0.984	-1.6	0.32	1.4	37	0.04	0.0681	0.06
	PBO	14	-0.02	1.065	-2.6	-0.21	1.9	14	0.13	0.1465	0.01

There was no meaningful difference in mean height (HAZ / HAP) or weight (WAZ / WAP) growth between the ETV and placebo groups while on entecavir/placebo therapy.

Discontinuation due to adverse events

No subjects in the integrated naive safety cohort or integrated experienced safety cohort discontinued study therapy due to AEs. Two subjects (3%) in the placebo group discontinued study therapy due to AEs (acute exacerbation of CHB and hepatic flare in 1 subject each)

Adverse events by age group

In both treatment groups, the rates of AEs were lowest among subjects in the oldest age cohort (>12 - < 18 years). In the ETV group, the proportion of subjects with AEs decreased with increasing age (23/27 subjects ≥2 - ≤6 years [85%], 19/31 subjects 6 - ≤12 years [61%], and 32/62 subjects > 12 - < 18 years [52%]). These differences seemed to be mainly due to the higher incidence of infections and respiratory AEs in the younger children.

There appeared no significant trend for adverse effects or laboratory abnormalities related to age.

2.5.2. Discussion and conclusion on clinical safety

The paediatric safety database comprises 173 patients treated with entecavir for a median of 60 weeks in the nucleoside naive cohort and 24 paediatric patients treated with entecavir for a median of 96 weeks in the nucleoside experienced cohort. The emerging safety profile is not clearly different from placebo. No paediatric specific or age specific safety concerns have been identified, though it is recognised that the safety database in the lowest age span (2-6 years) contained a total of 40 individuals, and that the safety database in the smallest children that would be encompassed by the indication is small. There was no consistent impact on growth. A follow up of five years from study start is anticipated.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

The RMP is acceptable with minor revisions required for the next update.

Version 11 of the RMP has been assessed in the context of the second round of a variation to extend the indication for use in the paediatric population.

There were no new identified or potential risks from the review of the efficacy and safety data for the 173 HBeAg positive nucleos(t)ide treatment-naïve patients treated with ETV for a median duration of 60 weeks submitted as the basis for this variation. Use in the paediatric population remains as "missing information" given that long-term data in this population is expected in Studies AI463028 and AI463189.

Included in the pharmacovigilance plan are the interim and final study reports for the 2b and 3 (-028 and -189) for the pivotal studies upon which the application for extension is based. Both studies have been designated as category I and therefore key to the benefit / risk.

Included in the risk minimisation plan are routine measures and the additional activities of a long term study and inclusion into a pregnancy registry. The MAH has included the aforementioned studies in the risk minimisation plan as "additional risk minimisation activities" which is inappropriate, as they are

pharmacovigilance activities. During the procedure the MAH introduced the requested changes in RMP version 12.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Summary of safety concerns	
Important Identified Risks	**Summary**
Exacerbation of Hepatitis	Acute exacerbation of hepatitis following withdrawal of therapy, while often asymptomatic, can be associated with severe complications, particularly in patients with advanced cirrhosis. In patients treated with LVD or ADV, these complications occasionally have resulted in death. During the clinical development of ETV, symptoms associated with withdrawal of ETV therapy have generally been benign. However, the frequency of severe complications following withdrawal of ETV may be greater in the post marketing period than during clinical studies, as a broader population of patients, including those with severe co morbidities, is exposed to the drug.
ETV Resistance	Antiviral resistance may result in a loss of clinical effect and potential transmission of resistant HBV. In LVD refractory patients, mutations in the HBV polymerase that encode LVDr substitutions may lead to the subsequent emergence of secondary substitutions, including those associated with ETVr. Patients with LVDr HBV are at higher risk of developing subsequent ETVr HBV than patients not previously treated with LVD. In addition, virological breakthrough can be associated with serious clinical complications of the underlying liver disease especially in decompensated patients. Subsequent rebound in viremia may be associated with ALT flares and disease progression to cirrhosis, hepatic decompensation, and HCC.
Emergence of resistant HIV in HIV/HBV co infected patients not concurrently receiving effective HIV treatment	Emergence of HIV resistance at M184 has been observed when ETV is used to treat CHB infection in HIV/HBV co infected patients who are not receiving concurrent effective HIV treatment. This resistance substitution is considered to have important clinical implications because it potentially limits future HIV treatment options (specifically it confers resistance to LVD and FTC, which are components of preferred and alternative ART regimens in ART naïve patients). In HIV/HBV co infected patients, ETV has only been studied clinically in patients receiving concomitant effective HIV therapy and has not been assessed in clinical trials for anti HIV clinical activity. ETV can select for a M184I substitution in vitro at micromolar concentrations, which confirms that ETV has the potential to exert inhibitory pressure on HIV replication. In addition, BMS has received post marketing reports of decreased HIV RNA, including patients who demonstrated increasing percentages of HIV RNA clones harboring the M184V mutation, in HIV/HBV co infected patients receiving ETV.
Important Potential Risks	
Carcinogenicity	Analyses of malignancies that have occurred during the clinical studies do not show an increase in human malignancies over the expected rate in patients with CHB or in the comparator group from clinical studies. The major limitation of the clinical studies analyses is that the lag period for detection of a malignancy following exposure to a carcinogen may exceed the

Summary of safety concerns	
Mitochondrial Toxicity	observation period of the ETV studies to date. The majority of patients have been observed up to 52 weeks. Additionally, relatively rare events are difficult to assess during clinical development related to the size of programs. Long term observational studies, specifically study 080, with larger populations enrolled will overcome these limitations. Mitochondrial toxicity is a recognized class effect of nucleos(t)ides. Within the class, the frequency of this event and its numerous manifestations are highly variable. This variability is partially related to the degree of binding to host g DNA polymerase by the nucleos(t)ide. Other factors influencing frequency are female gender, obesity, pregnancy and, specifically for HIV infected patients, low CD4 count. The characteristics of ETV, i.e., its low binding affinity for DNA polymerase and no effect on oxidative metabolism in HepG2 cells, predict that mitochondrial toxicity related to ETV will be low compared to other nucleos(t)ide. The human experience to date is consistent with these models; mitochondrial toxicity is rare.
Missing Information Long term safety and clinical outcomes data	Three ETV studies (AI463049, AI463080, and AI463901) allow for long term follow up of ETV treated patients, to assess for potential risk of malignant neoplasms and other long term complications. Long term safety Study AI463080 is ongoing. Studies AI463049 and AI463901 have been completed; the final clinical study reports (CSRs) have been submitted.
Use in the pediatric population	Long-term follow up of safety and efficacy in Studies AI463028 and AI463189 will be completed as per current post-approval measures from the CHMP.
Use in pregnancy	There are no adequate and well-controlled studies in pregnant women. ETV should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women of child-bearing potential should use effective contraception.
Use in elderly patients (≥65 years of age)	Clinical studies of ETV did not include sufficient numbers of subjects aged ≥ 65 years to determine whether they respond differently from younger subjects. The PK profile of ETV does not differ by age. No dosage adjustment of ETV based on age is required. However, ETV is substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in elderly patients since they are more likely to have decreased renal function; dosage adjustment is recommended for patients with creatinine clearance < 50 mL/minute, including patients on hemodialysis or continuous ambulatory peritoneal dialysis.
Use in severe acute exacerbation of CHB	A publication by Wong et al. identified a higher 1 year mortality rate with ETV when compared to LVD in a specific subset of patients with spontaneous severe acute exacerbation of CHB. BMS has continued to review the literature during its routine PhV activities in order to identify other relevant publications. No further publications have been identified that indicate a potential for increase in liver specific mortality with ETV treatment.

Pharmacovigilance plans

Study (type and study number)	Safety concern addressed	Planned date for submission of interim or final reports
Ongoing studies		
AI463028: Phase 2b, open-label study to determine the doses of ETV in children and adolescents that produce drug exposures comparable to those observed in adults given the 0.5 mg and 1.0 mg doses	Pediatric use and long-term follow up of safety and treatment outcomes	Interim CSR (120-weeks) Dec 2013 Final CSR (cohort A+B) 3Q2016
AI463080: Phase 4, randomized, observational study. Long-term study of ETV versus other standard of care HBV nucleos(t)ide analogues to prospectively assess the rates of malignant neoplasm, HCC, non-HCC liver-related events of HBV disease progression, and mortality in the 2 treatment groups.	Assess rates of malignant neoplasms	Final CSR 4Q2017
AI463189: Phase 3, comparative, randomized, double-blinded, placebo-control, multi-center study to compare the proportion of subjects in each group who achieve a combination of HBV DNA suppression and HBeAg seroconversion at Week 48.	Pediatric use and long-term follow up of safety and treatment outcomes	Interim CSR (48 weeks; 180 patients) 3Q2014 Interim CSR (192 weeks) 3Q2017 Final CSR 4Q2019

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Exacerbation of Hepatitis	SmPC, Routine PhV	None
ETV Resistance	SmPC, Routine PhV	None
Emergence of resistant HIV in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment	SmPC, Routine PhV	DHP letter 2007
Carcinogenicity	SmPC, Routine PhV	None
Mitochondrial Toxicity	SmPC, Routine PhV	None
Long-term Safety and Clinical Outcomes Data	Routine PhV	None
Use in the Pediatric Population	SmPC, Routine PhV	None
Use in Pregnancy and Lactation	SmPC, Routine PhV	None
Use in Elderly Patients (≥ 65 years of age)	SmPC, Routine PhV	None
Use in severe acute exacerbation of CHB.	Routine PhV	None

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2, of the SmPC have been updated. The Package Leaflet has been updated accordingly.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The applicant has performed two paediatric studies – AI463028 in which the primary concern was to confirm that selected doses would give comparable exposure in children 2-18 years of age, as does the labelled dose in adults. The data provided support the achievement of the primary goal. Following this, the MAH is performing the AI463189 study in nucleos(t)ide naive children that are HBeAg+ and have persistently elevated ALT, where entecavir therapy is compared with placebo. At 48 weeks superiority against placebo was shown on the primary endpoint, a composite of plasma HBV-DNA <50 IU/mL and HBeAg seroconversion at week 48. Twenty-four percent (20/82) of patients treated with entecavir reached this endpoint compared to 2 % (2/41) of placebo-treated patients. The difference in proportions was 20.2 (95%CI 9.1-31.4%). The proportion of patients with HBV-DNA <50IU/mL was 46.3% in the entecavir group, compared to 2.4% in the placebo group. The difference in proportions was 41.8% (95%CI 29.4-54.2%). The proportion of patients with HBeAg seroconversion was 24% in the entecavir arm versus 12% in the placebo arm. The difference in proportions was 12.1% with a 95% CI from -1.5-25.7%, and thus of borderline statistical significance. Furthermore, the proportion of patients with ALT normalisation was 67% (55/82) in the entecavir arm compared to 22% (9/41) in the placebo arm. No subjects were shown to have developed entecavir resistance after one year of therapy, whereas one patient had developed partial resistance to entecavir at 96 weeks. These data are compatible with a similar resistance barrier as seen in adults, and are indicative that the therapeutic effect of entecavir is durable provided that adherence is sufficient.

Uncertainty in the knowledge about the beneficial effects

It is notable that while the study aimed at including paediatric patients with immune active disease, only a limited number of biopsies were performed before inclusion in the study (40 had a prior liver biopsy done as part of their CHB management). It is nevertheless acknowledged that liver biopsy (invasive procedure) is not universally performed prior to paediatric treatment. The ALT criterion allowed for inclusion of patients with ALT > 1.5 × ULN at screening and at least on 1 other occasion within 8 to 24 weeks prior to screening. This is less stringent than the indication for treatment according to ESPHGAN guidelines (Jonas et al, J Hepatol 2013), which in the general case require elevated ALT for more than six months in HbeAg+ patients, in order to initiate therapy.

In most cases, chronic hepatitis B is clinically benign during childhood. The outcome measures of the performed study are primarily virological. The precise role and benefit of antiviral therapy for chronic hepatitis B in children appears not to have been fully defined in longitudinal studies.

Notable findings in the pivotal, placebo controlled AI463189 study include a lower antiviral efficacy (lower decrease in HBV-DNA and lower proportion of patients with HBV-DNA <50 IU/mL) than in the pivotal adult study of a comparable population. Furthermore, the proportion of patients with suppressed HBV-DNA was considerably lower in Europe compared to Asia or North America.

Particularly, it is notable that efficacy against genotype D virus (prevalent in Europe) was very low, with only 16% reaching plasma HBV-DNA <50 IU/mL at week 48, compared to 50-73% in other genotypes. However, at week 96 this proportion was 39%. No patient with genotype D at baseline developed drug resistance. Notably, the in vitro susceptibility to entecavir of genotype D is similar to that of the other genotypes, and there is no general support outside the AI463189 study for a differential, lower effect of entecavir in genotype D. All in all, the reasons for the low response in this genotype in the AI463189 are not fully understood. Notably, they are confounded by high baseline viral load in patients with this genotype in the small sample of this trial (a finding that is not supported by data across cohorts and study).

Risks

Unfavourable effects

The paediatric safety database comprises 173 patients treated with entecavir for a median of 60 weeks in the nucleoside naive cohort and 24 paediatric patients treated with entecavir for a median of 96 weeks in the nucleoside experienced cohort. The side effect profile of entecavir in children was not different from that observed in adults. No paediatric specific safety concerns have been identified. There was no consistent on-treatment impact on growth.

Uncertainty in the knowledge about the unfavourable effects

The safety profile of entecavir in the lowest age stratum (2-6 years) did not markedly differ from placebo. There are no outstanding adult safety issues that would be of particular concern for the very smallest children within the proposed age range for the indication. Further, the anticipated entecavir exposure in this stratum at the selected dose is similar to that in nucleoside naive adults. Still, the total safety database in this age band and thus in the smallest children for whom the indication would pertain, is relatively low (n=40 in the nucleoside naive cohort), which per se gives rise to some residual uncertainty.

Regarding preclinical studies, no new findings relevant for clinical safety assessment were observed in juvenile rats at an exposure well over clinical exposure. A reduced acoustic startle response was noted during the recovery period, but not during the treating period, in both male and female rats at 10 mg/kg. The clinical significance of this finding is not fully clear, but is deemed of unlikely clinical significance.

A follow up of five years from study start is anticipated to further investigate any potential impact of prolonged entecavir exposure on growth and increase the available safety database.

In addition to those data, it has to be reminded that based on the carcinogenicity in rodents, entecavir was shown as having a carcinogenic potential. The study in paediatric patients was agreed by the PDCO considering that while the long term risk for carcinogenesis was unknown, there was no evidence to suggest that paediatric patients would be at a higher risk for malignancy than adults. A dedicated long term outcomes study AI 463080 is ongoing in adults, designed to enroll a total of 12 500 treated patients (1:1 entecavir versus other anti-HBV drugs). Based on the sixth interim progress report (66 months of cumulative study data), there is no general signal of a higher malignancy risk in patients randomised to ETV compared to non ETV treatment.

Benefit-risk balance

It is acknowledged that the majority of young children are in the immune tolerant phase and there is currently no established benefit for the treatment of children in this stage of disease. However, others will enter the immune-active phase and potentially develop severe complications of the CHB during childhood. While it is notable that the younger the patient group, a smaller proportion would fulfil these criteria, it is also notable that age per se is not a determinant for the treatment decision, according to therapeutic guidelines.

The paediatric indication suggested after review is: “for the treatment of chronic HBV infection in nucleoside naive paediatric patients from 2 to < 18 years of age with compensated liver disease who have evidence of active viral replication and persistently elevated serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis. With respect to the decision to initiate treatment in paediatric patients, see sections 4.2, 4.4, and 5.1.”

While therapeutic guidelines support the need for histological data in the decision making process for initiation of therapy in paediatric patients, it is recognized that unlike in adults, for whom non-invasive tests can be performed, non-invasive methods for fibrosis assessment have not been validated in children. Given the invasive nature of the liver biopsy, it might not be always applicable in clinical practice. It is therefore not considered a mandatory criterion for treatment initiation in the product information. This nevertheless emphasize that the decision to treat paediatric patients should be based on careful consideration of individual patient needs and with reference to current paediatric treatment guidelines including the value of baseline histological information.

Due to an impaired barrier to resistance, entecavir efficacy is not durable in patients with selection of resistance due to prior exposure to a cross-resistant drug, with 50% of such patients developing resistance within five years in the long term follow up of the pivotal adult study. Therefore, entecavir is not suitable for paediatric patients with such a treatment history.

The applicant has demonstrated that the paediatric dose provides similar exposure in the relevant paediatric age bands as does the licensed adult dose for nucleoside naive patients. In the trial, entecavir was given in the fasted state, bioavailability being somewhat lower when taken with food. As required intake in fasting may be a problem, particularly in small children, and may impact adherence, an adjusted posology has been developed based on PK modelling, which will allow for intake with food.

The applicant has also shown that the selected dose in nucleoside naive patients produces an antiviral effect that is greater than placebo, though estimates of efficacy are lower than in comparable adult patients, for reasons that are presently not clear. As the pharmacological target of entecavir is viral, it is similar in adults and children; therefore similar exposure would be expected to yield similar effects. That said, it is recognised that host factors (e.g., immune related) may affect summary response to treatment, as evidenced by the impact of ALT levels on response. The paediatric efficacy demonstration was performed in HBeAg+ patients. These have higher levels of viremia and are on the “difficult to treat” spectrum, compared to HBeAg- patients. As the common denominator in paediatric treatment of CHB according to European professional society guidelines is chronic, active hepatitis with significant viral replication, it appears that the antiviral benefits shown in the HBeAg+ population can be extrapolated to the HBeAg-, as proposed by the MAH.

The clinical benefit of viral suppression has been shown in adults. While it is recognised that benefits in paediatric patients are less well defined, the use of entecavir according to label, in accordance with expert opinion on paediatric antiviral treatment, is recognised. No adverse effects or risks have been demonstrated that would outweigh such anticipated benefits. The benefit of entecavir in nucleoside-

naive patients, as proposed, is positive. The MAH has provided information in the SmPC on parameters needed to consider when deciding to commence therapy in paediatric patients, as well as references to expert guidelines. This includes recommendations on the duration of continued therapy after HBeAg seroconversion. Within the scope of this variation, recommendations on this issue for adults are also updated in the product information in accordance with professional society guidelines.

4. Recommendations

☒ The application for the extension of indication to include treatment of chronic HBV infection in paediatric patients from 2 to <18 years of age with compensated liver disease and evidence of active viral replication and persistently elevated serum ALT levels, is approvable since other concerns and major objections have all been resolved.

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variations requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include treatment of chronic HBV infection in nucleoside naive paediatric patients from 2 to < 18 years of age with compensated liver disease who have evidence of active viral replication and persistently elevated serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis.

Consequently, the MAH proposed the update of sections 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

The variation proposed amendments to the SmPC and Package Leaflet.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0125/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate in the Package Leaflet.