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SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation Division

# Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

**Sebivo**

**International non-proprietary name: telbivudine**

**Procedure no.: EMA/H/C/00713/P46/0057**



## Note

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

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# 1. INTRODUCTION

Novartis Europharm Ltd submitted the **final report for the SEBIVO Study CLDT600A2104,** *an open-label, single dose study to evaluate the pharmacockinetics, safety and tolerability in children and adolescents with compensated HBeAg-positive chronic hepatitis B virus infection***, in accordance with Article 46 of Regulation** (EC) No 1901/2006, as amended.

A short critical expert overview has also been provided.

Novartis Europharm Ltd stated that Study CLDT600A2104 is part of a paediatric clinical development program (EMEA-00065-PIP01-07-M02). In accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for SEBIVO and therefore do not require taking further regulatory action on the marketing authorisation for SEBIVO at the time being.

# 2. SCIENTIFIC DISCUSSION

## *2.1. Information on the development program*

*- Introduction*

Telbivudine (β-L-2'-deoxythymidine; LDT), is a deoxynucleoside with the L configuration of thymidine. The presence of a hydroxyl group in the 3'-position (3' OH) of the β-L-2'- deoxyribose sugar confers activity exclusively against hepadnaviruses, including hepatitis B virus (HBV), woodchuck hepatitis virus (WHV), and duck hepatitis B virus (DHBV).

Sebivo was first registered in Ghana on 13 Jul 2006 and received market authorization in Switzerland on 21 Aug 2006, (the latter date is considered to be the international birth date of the product). Marketing Authorization was granted in Europe on 24 April 2007 and renewed in April 2012.

At the time of the Renewal in EU **the indication for SEBIVO has been restricted for patients for whom an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate.**

The product is currently approved in 108 countries worldwide and is available as a tablet or as an oral solution.

*- Paediatric development program:*

**Line listing of all the concerned clinical studies:**

| Type of study | status |
|---|---|
| Study 3: CLDT600A2104:<br>Open-label, single dose study to evaluate pharmacokinetics, safety and tolerability | Completed<br>Being Submitted |
| Study 4: CLDT600A2306:<br>Randomised, double-blind, placebo-controlled, multi-center study to evaluate pharmacokinetics, efficacy and safety of telbivudine in children and adolescents with compensated HBeAg-positive chronic hepatitis B virus infection in patients aged from 2 to less than 18 years | Planned<br>→ currently under review in a Request for Modification, with PDCO opinion in September 2012 |
| Study 5: CLDT600A2YYY:<br>→ currently under review in a Request for Modification with PDCO opinion Sep 2012<br>Randomised open label multicentre study to evaluate efficacy and safety, of telbivudine in children and adolescents with compensated HBeAg-negative chronic hepatitis B virus infection in patients aged from 2 to less than 18 years | Planned<br>→ currently under review in a Request for Modification, with PDCO opinion in September 2012 |
| Study 6: CLDT600A2414:<br>A cross-sectional, multi-center retrospective data collection study in Western and Asian countries in children and adolescents with chronic hepatits B virus infection in patients aged 2- <18 years | completed |

*Rapporteur's note*: *study A2414 was an epidemiology phase IV survey which aimed at assessing the feasibility and design of future study. Telbivudine was not administered in this study.*

- Purpose of the submission

Novartis has recently completed (last patient last visit on 28 March 2012) study CLDT600A2104, an open-label, single-dose study to evaluate the pharmacokinetics safety and tolerability in children and adolescents with compensated HBeAg-positive chronic hepatitis B virus infection. The last patient last visit date is defined by the date when also US FDA approved to the changes to the study protocol which had been proposed to PDCO in the Request for Modification of the approved PIP EMEA-000065-PIP01-07-M02.

**Indeed, due to slow enrolment, in agreement with both Agencies, the study was terminated after enrolment of 23 out of the planned 28 patients as the study met its primary objective.**

This study has been conducted as part of the paediatric investigational plan agreed for Sebivo (telbivudine) on 17 October 2008, and modified in the Request for Modification of the agreed PIP with opinion on 15 July 2011.

The results of this study are now submitted to the CHMP according to Article 46 of Regulation (EC) No 1901/2006 which requires that any marketing authorization holder sponsored study which involves the use in the paediatric population of a medicinal product covered by a marketing authorization, whether or not they are conducted in compliance with an agreed paediatric investigation plan, is to be submitted to the competent authority within six months of completion of the study concerned.

**The current submission presents the pharmacokinetic and safety data derived from 23 HBV-infected children and adolescent aged 2-18 years who received single dose of telbivudine in study CLDT600A2104.**

## *2.2. Clinical aspects*

CLDT600A2104 is a **first-in-pediatrics study (open-label, single-dose)** assessing the safety, tolerability and PK of a single dose of telbivudine (LDT600) in HBV-infected children and adolescents aged 2-18 years.

| | |
|---|---|
| **Title** | A **Phase I, Open-Label, Single-Dose** Study to Evaluate the Pharmacokinetics and Safety of Telbivudine (LDT) in Children and Adolescents with Chronic Hepatitis B |
| **Study centers** | 11 study centers: Belgium (1), Germany (3), UK (2), Bulgaria (2), Egypt (1), Philippines (2) |
| **Study start Date**<br>**Data cut-off** | 5 Feb 2009 (First patient first visit)<br>27 Nov 2011 (last patient last visit)<br>8 Mar 2012 (early termination date) |
| **Study population** | Children and adolescents 2 to 18 years old with documented CHB infection and HBsAg positivity at screening. Patients were required to have body weight within 15th to 85th percentile of normal relative to age, screening creatinine clearance (CLcr) ≥ 80 mL/min/1.73 m2, and all female patients of reproductive potential were to have a negative serum pregnancy test at screening and a negative urine pregnancy test on Day –1.<br>Patients with decompensated liver disease or other clinically significant condition were excluded from the study. Patients who had been treated with interferon within six months of screening, nucleos(t)ide reverse transcriptase inhibitors within three months of screening, or any other antiviral therapy within 30 days of study drug dosing were also excluded. |
| **Number of patients** | **Planned: 28**<br>were to be stratified into age groups 2-<6 years old (N=12), 6-12 years old (N=8) and 13-18 years old (N=8)<br>**Enrolled: 23**<br>Enrollment was slower than anticipated and study was terminated after enrollment of 23 out of the planned 28 patients, as it had met its primary objective. The number of patients in the **2-<6 years of age stratum was therefore less than planned (N=7**). All enrolled patients were included in the PK and safety analysis sets. |
| **Dose** | Patients received a single dose of 15 mg/kg, 25 mg/kg or 600 mg LDT600. Total dose did not exceed 600 mg. |
| **PK analysis** | Blood samples (1.0 mL whole blood to generate ~0.5 mL plasma at each time point) for the<br>determination of plasma levels of LDT600 were collected in heparinized Vacutainer® tubes prior to (predose) and after dosing at 1, 2, 3, 4, 8, 12, 24, 48, 72 and 120 hours.<br>PK parameters, including Cmax, Tmax, AUC0-24h, AUC0-t, AUCinf, CL/F, Vz/F, λz and T1/2, were derived from LDT600 plasma concentration versus time profiles. |

**Study design:**

This is a Phase I, open-label, single-dose study to evaluate the pharmacokinetics and safety of LDT600 in pediatric and adolescent patients with chronic HBV infection. Eligible pediatric and adolescent (patients of 2-18 years of age) will be stratified into three age groups.

The study started enrollment with the oldest children and, after assessment of safety, proceeded to each subsequent younger age cohort. The strata were:

- Stratum 1: 2- <6 years old (N=12)
  - Substrata 2- <4 year (n=4) and 4- <6 year (n=8);
- Stratum 2: 6- <12 years old (N=8)
  - Substrata 6- <9 year (n=4) and 9- <12 year (n=4);
- Stratum 3: 13-18 years old (N=8).

The study started with the adolescent patients in Stratum 3 who received a single dose of 600 mg LDT600 as an oral solution. The first half (n=4) of Stratum 2 received a single 15 mg/kg dose of LDT600 as an oral solution following review of Stratum 3 safety and pharmacokinetic parameters. The second half (n=4) of Stratum 2 and the first half of Stratum 1 (n=6) received a single 15 mg/kg dose of LDT600 as an oral solution following review of Stratum 2 (n=4) safety and pharmacokinetic parameters, respectively. There was a single patient in Stratum 1 (of the planned 6; see below) who received a 25 mg/kg dose of LDT600 as an oral solution following review of Stratum 1 (15 mg/kg) safety and pharmacokinetic parameters.

**Dose selection to be used in the current Phase I PK study**

The LDT600 dose selected for adolescents (Stratum 3: 13-18 years old) is 600 mg/day. This was the dose used in the pivotal global Phase III trials of LDT600 in HBV-infected adult patients with compensated (NV-02B-007) and decompensated (NV-02B-011) liver disease. Children up to 12 years of age (Strata 1 and 2) will receive doses based on body weight with a maximum dose not to exceed 600 mg/day.

LDT600 is a nucleoside analogue that is predominantly eliminated via renal clearance; therefore, the PK of LDT600 depends on renal function. Pediatric populations are known to exhibit rapid developmental changes in renal function with higher CLcr normalized to body surface area (BSA) for younger age, which progressively decreases with age and approaches adult values about age 10-12 years. Given these considerations, higher per kilogram doses of LDT600 are expected to be needed for the pediatric population of 2–12 years of age while adolescents can be administered a full adult dose of LDT600 (600 mg).

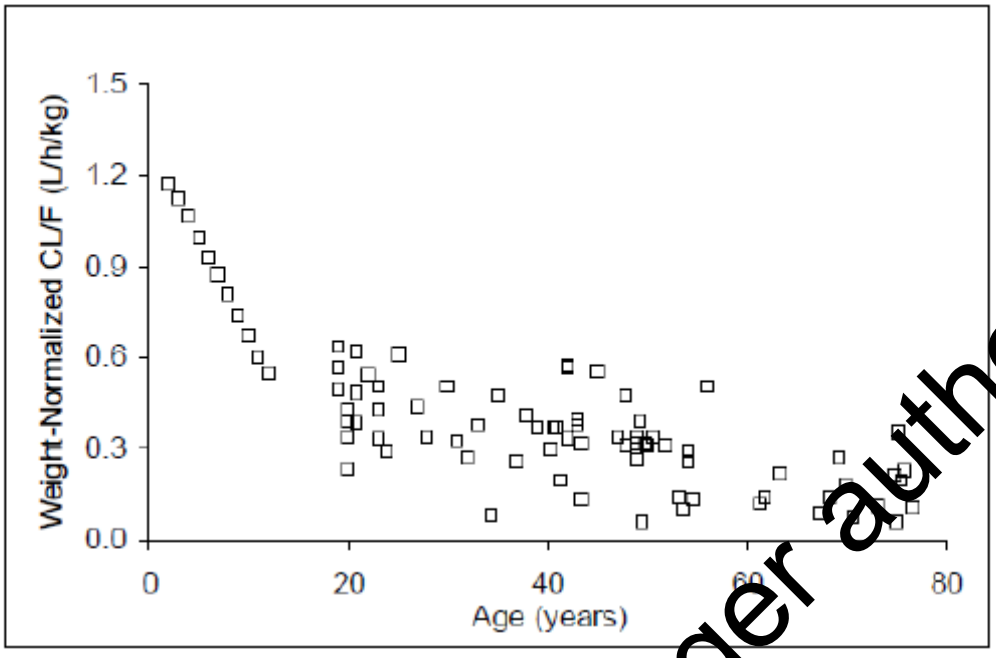
The doses of LDT600 used in the current single-dose PK study in pediatric patients were predicted based on available adult PK data so that the selected doses would produce plasma drug exposures (AUC) in the studied populations comparable to adult patients treated with the full dose of the drug (600 mg).

Given the absence of prior knowledge of LDT600 PK in children, the following assumptions have been made:

1. LDT600 CL/F is a linear function of the estimated CLcr.
2. LDT600 PK are dose-proportional in the target pediatric (2–12 years of age) and adolescent (13–18 years of age) populations.
3. The oral bioavailability of LDT600 is similar in pediatric and adolescent populations to adults.

As shown in Figure 9-3, LDT600 CL/F (normalized to body weight) quickly falls from about 1.2 L/hr/kg to about 0.6 L/hr/kg as children grow from 2 to 12 years, then stabilizes with CL/F close to adult value. The median LDT600 CL/F for the 2- to 6-year-old group is 1.06 L/h/kg and for the 7- to 12-year-old group is 0.570 L/h/kg, which is about 3- and 2-fold greater, respectively, than the median adult LDT600 CL/F of 0.33 L/hr/kg. As can be seen from Figure 9-3, the weight-normalized LDT600 CL/F in adolescents is comparable to adults.

Figure 9-3 LDT CL/F (normalized to body weight) versus age




The following doses were selected for the current single-dose PK study for the pediatric populations of 2–12 years of age: **15 and 25 mg/kg (450 and 600 mg/m2) with a maximum dose not to exceed 600 mg. For adolescent patients of 13–16 years of age, a 600-mg dose will be administered**.

Of note, the selected LDT600 pediatric doses, 2- to 3-fold times the adult dose, are therefore comparable to lamivudine and adefovir, drugs that are also predominately eliminated via renal clearance.

**Study patients**

Enrolment in the study was slower than anticipated despite the use of multiple sites in multiple countries selected for presence of pediatric HBV infection. After 22 patients had been recruited and completed the study, a preliminary analysis of PK and AEs was performed. A summary of this preliminary analysis with a pediatric dose recommendation was shared by Novartis with PDCO and US FDA. Based on these interactions there was agreement with both Agencies on early study closure (EU: EMEA-00065-PIP01-07-M02; US: Written Request Amendment #3). The study was terminated after enrolment of 23 out of the planned 28 patients as the study had met its primary objective.

Of the 23 patients enrolled, 10 were assigned to receive LDT600 (15 mg/kg), 5 to receive LDT600 (25 mg/kg) and 8 to receive LDT600 (600 mg). All patients (100%) received the planned LDT600 dose and completed the study.

Table 10-1 Patient disposition – n (%) of patients (all patients)

| | LDT600 15mg/kg N=10 | LDT600 25mg/kg N=5 | LDT600 600mg N=8 | All Treatments N=23 |
|---|---|---|---|---|
| Patients | | | | |
| Completed | 10 (100.0) | 5 (100.0) | 8 (100.0) | 23 (100.0) |

A total of 7 patients were in the 2<6 years old age stratum, 8 in the 6-12 years old age stratum and 8 in the 13-18 years old age stratum.

The subjects 13 to 18 years of age all received 600 mg LDT600 oral solution. This group was predominantly male (75%) and the majority of the patients were Asian (75%). Children from 2 to 12 years of age received either 15 mg/kg or 25 mg/kg of LDT600 oral solution. Children in the 2-<6 year age group were primarily female (71.4%) and Caucasian (85.7%), while patients in the 6-12 year age group were equally male and female (50%) and represented both Caucasian (37.5%) and Asian (50%) races.

**Pharmacokinetics**

The single dose pharmacokinetics data obtained in the LDT600A2104 study (with the historical comparison data from adults) are summarized in the following table:

**Pharmacokinetic parameters of LDT600 after a single oral dose in HBV-infected pediatric patients and in comparison to a historical study of healthy adults**

| PK parameter | $T_{max}$ (h) | $C_{max}$ (ng/mL) | $AUC_{0-24h}$ (ng.h/mL) | $AUC_{0-t}$ (ng.h/mL) | $AUC_{inf}$ (ng.h/mL) | $T_{1/2}$ (h) | CL/F (mL/hr) |
|---|---|---|---|---|---|---|---|
| **13-18 years 600 mg; n=8** | | | | | | | |
| Mean | - | 3510 | 22300 | 26800 | 27700 | 38.7 | 23200 |
| SD | - | 1190 | 5720 | 6590. | 6830 | 7.42 | 7660 |
| CV% mean | - | 33.9 | 25.7 | 24.6 | 24.6 | 19.1 | 33.0 |
| Geo-mean | - | 3340 | 21600 | 26000 | 26900 | 38.2 | 22300 |
| CV% geo-mean | - | 34.1 | 28.4 | 29.2 | 28.8 | 18.2 | 28.8 |
| Median | 2.59 | 3500 | 21500 | 27300 | 28100 | 36.2 | 21400 |
| [Min; Max] | [1.97; 4.00] | [ 2250; 5710] | [12600; 30800] | [15000; 32600] | [14700; 37500] | [29.7; 53.7] | [16000; 40700] |
| **6-12 years 15 mg/kg; n=4** | | | | | | | |
| Mean | - | 3290 | 17600 | 20700 | 21500 | 36.3 | 19200 |
| SD | - | 748 | 3400 | 4550 | 4610 | 6.81 | 2060 |
| CV% mean | - | 22.7 | 19.3 | 22.0 | 21.5 | 18.7 | 10.7 |
| Geo-mean | - | 3230 | 17400 | 20300 | 21100 | 35.8 | 19100 |
| CV% geo-mean | - | 21.1 | 20.0 | 22.6 | 22.0 | 20.4 | 10.8 |
| Median | 2.53 | 3080 | 17900 | 20700 | 21400 | 38.0 | 19100 |
| [Min; Max] | [1.83; 3.00] | [2800; 4400] | [13800; 20800] | [15900; 25600] | [16600; 26500] | [26.9; 42.4] | [17000; 21500] |
| **6-12 years 25 mg/kg; n=4** | | | | | | | |
| Mean | - | 5430 | 33100 | 39700 | 40500 | 28.0 | 15000 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| SD | - | 1530 | 9530 | 9760 | 9680 | 7.03 | 3820 |
| CV% mean | - | 28.2 | 28.8 | 24.6 | 23.9 | 25.1 | 25.4 |
| Geo-mean | - | 5260 | 32200 | 38900 | 39700 | 27.3 | 14600 |
| CV% geo-mean | - | 30.1 | 27.8 | 23.4 | 22.7 | 27.9 | 29.3 |
| Median | 2.48 | 5570 | 30700 | 36600 | 37500 | 29.5 | 16100 |
| [Min; Max] | [1.92; 3.00] | [3740; 6840] | [24800; 46400] | [32000; 53600] | [32700; 54400] | [18.8; 34.2] | [9660; 18300] |
| **2-<6 years 15 mg/kg; n=6** | | | | | | | |
| Mean | - | 2910 | 17900 | 21200 | 22100 | 29.9 | 15200 |
| SD | - | 453 | 3550 | 4520 | 4760 | 10.5 | 5920 |
| CV% mean | - | 15.6 | 19.8 | 21.3 | 21.6 | 35.2 | 39.0 |
| Geo-mean | - | 2870 | 17600 | 20800 | 21700 | 28.3 | 14000 |
| CV% geo-mean | - | 17.3 | 20.9 | 21.1 | 20.9 | 39.0 | 48 |
| Median | 2.00 | 3060 | 17500 | 20400 | 20900 | 29.8 | 15400 |
| [Min; Max] | [1.28; 3.03] | [2080; 3320] | [12600; 21900] | [16000; 28400] | [17000; 30100] | [16.5; 41.9 | [6490; 22300] |
| **2-<6 years 25 mg/kg; n=1** | | | | | | | |
| Mean | 4.00 | 2440 | 15300 | 19900 | 20400 | 18.3 | 17100 |
| **Adult 600 mg oral solution (n=23)** | | | | | | | |
| Mean | - | 3456 | 25437 | 30752 | 32418 | 43.8 | - |
| SD | - | 1170 | 7457 | 8032 | 8441 | 11.1 | - |
| CV% mean | - | 33.9 | 29.3 | 26.1 | 26.0 | 25.3 | - |
| Median | 3.00 | | | | | | |
| [Min; Max] | [2.00; 6.00] | | | | | | |

Plasma concentration-time profiles and systemic exposures (Cmax and AUC) of LDT600 were comparable between adults and children age 13-18 years old following a single 600 mg dose of oral solution formulation.

However, plasma exposures in children age 6-12 years were lower at the 15 mg/kg dose (~33% in AUC) and higher at the 25 mg/kg dose (~28% in AUC) when compared to adults receiving 600 mg LDT600.

Plasma exposures were similar between children age 2-<6 years and age 6-12 years after receiving a single 15 mg/kg dose of LDT600. Dose proportional increases in Cmax and AUC were observed in children age 6-12 years when the dose increased from 15 mg/kg to 25 mg/kg. As one child in the 2-<6 year age group received the 25 mg/kg dose, proportionality could not be assessed.

Compartmental analysis of the single dose data from the enrolled children was performed to predict the steady state exposure of LDT600 in pediatric patients based on the above PK data.

**Plasma LDT600 concentration versus time profiles for children aged 2 to 12 years administered a single 15 mg/kg dose of LDT600 and for children aged 13 to 18 years administered a single 600 mg of LDT600 were fitted to a two-compartment 1st order, microconstant, lag time, 1st order elimination PK model (WinNolin version 5.2).** Following 20 mg/kg/day and 600 mg/day oral administration for children age 2 to 12 years and children age 13 to 18 years, respectively, the model predicted systemic, steady state LDT600 exposures that closely matched those observed in healthy adults receiving 600 mg of LDT600 once daily.

The summary predicted steady state pharmacokinetic parameters for all the children as compared to the target exposure in adults receiving the approved dose of 600mg/d is presented in the following table:

**Comparison of predicted LDT600 pharmacokinetics at the steady state in children age 2 to 18 years to a historical study of healthy adults**

| PK parameters | Dose | $T_{max}$ (h) | $C_{max}$ (ng/mL) | $AUC_{0-24h}$ (ng.h/mL) | $C_{trough}$ (ng/mL) |
|---|---|---|---|---|---|
| Adults[a] | 600 mg/day | 2 (1-4)[b] | 3690±1250 | 26100±7200 | 200-300 |
| Children (2 to 12 years) | 20 mg/kg/day | 2.10 | 3750±1120[c] | 28300±8490[c] | 268-280 |
| Children (13 to 18 years) | 600 mg/day | 2.16 | 3340±1000[c] | 25070±7520[c] | 227-244 |

[a]All values from US label. [b]Mean (range). [c]Estimation of SD based on typical interpatient variability (CV 30%) for LDT600.

The study result of a **daily dose of 20 mg/kg for children was in the middle of the range predicted by comparing the telbivudine CL/F in children and adults** based on previous experience with extrapolation of renally excreted nucleosides, such as lamivudine, from adults to children. In adults, a 600 mg dose (average 7.5 mg/kg) of telbivudine produces an AUC0-∞ of approximately 23,000 ng/ml*h (AUC0-24h, ~20,000 ng/ml*h). To achieve similar exposures in children 2-6 years old, a weight-based dose of 21–27 mg/kg was predicted; for the 7–12 year age group a dose of 13–20 mg/kg was proposed. The full analysis with the final data on all 23 subjects agrees with the preliminary analysis that a dose of 20 mg/kg up to a total of 600 mg of telbivudine will result in similar exposure in children from age 2-18 years as observed in previous clinical studies conducted in adults receiving the marketed dose of 600 mg/day. This assessment is based on the plasma exposure results from all the children, the linear pharmacokinetics of telbivudine, and extrapolation of the data by standard pharmacokinetic modeling methods.

**Safety**

There were no significant safety findings after administration of single oral dose of telbivudine in this study. Among the 23 patients who received telbivudine, with doses ranging from 15 mg/kg to 600 mg, 4 patients (17.4%) experienced an AE. All AEs were mild and none occurred in more than one patient; skin lesions, pruritus, protein in urine and malaise were suspected to be related to the study drug. No deaths or SAEs were reported in the study and no patient discontinued due to an AE.

**Efficacy**

No pediatric efficacy studies have been performed.

**To conclude**, the MAH considers that **a dose of 20 mg/kg per day (up to a maximum of 600 mg per day) of telbivudine is recommended for pediatric use**, as this resulted in plasma exposure similar to that seen in historical comparison to a healthy adult population receiving the marketed dose of 600 mg per day.

The dosing recommendation resulting from this study **will be used as the basis for the pediatric Phase III study.**

# 3. Rapporteur's Overall Conclusion and Recommendation

In accordance with Article 46 of Regulation (EC) n°1901/2006, Novartis is submitting the final report for the SEBIVO study CLDT600A2104. This is a first-in-pediatrics study assessing the safety and PK of a single dose of telbivudine in HBV-infected children and adolescents aged 2-18 years. A total of 28 paediatrics patients were planned to be included in the study. However, due to slow enrolment (despite the use of multiple sites in multiple countries), the study was terminated early after enrolment of 23 children (in agreement with both FDA and PDCO) as the study met its primary objective.

The enrolment in the study was staged with first enrolment of older children**. Due to slow enrolment leading to early termination, only 7 children out of the 12 planned in the 2-<6 years of age stratum participated in the study. As a consequence, only 1 children aged 2-<6 years old received the tested 25mg/kg dose and this dose was not taken into account in the PK modelisation**.

Overall the MAH rational to select the 20mg/kg dose (up to a maximum of 600mg/day) for children aged 2 to 12 years based on the study data and extrapolation from PK modeling **appears reasonable.** However, whether this dose is appropriate for children aged 2-6 years remains questionable due to the limitation of the PK data available in this age stratum (notably only 1 patient received the highest tested dose). Of note, in the HEPSERA pediatric development, a 0.25mg/kg dose was selected for children 7-11 whereas a somewhat higher 0.3mg/kg dose was selected for children aged 2-6.

The MAH choose the 20mg/kg dose for phase III study. Even though it is anticipated that the MAH will also face difficulties in recruitment of children aged 2-6 years old in phase III study, particular attention will have to be paid on the adequacy of this dose in those children.

As a general comment, the indication of SEBIVO (currently only in adults) has been restricted in Europe since it was considered that due to the low genetic barrier to resistance of SEBIVO, the benefit risk balance could only be considered positive when the use of an alternative antiviral agent with a higher genetic barrier is not available or appropriate. It has to be underlined that the place of telbivudine in HBV-infected children in Europe is questionable, even though at this time, only VIREAD is indicated in HBV-infected adolescents.

- **Recommendation**

☒ **Fulfilled –**