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 –**