DISCUSSION AND OVERALL CONCLUSIONS

The study was a Phase II study to evaluate the efficacy and safety of several infusions of HepaStem in UCD patients aged below 12 years old. The study was prematurely stopped by the sponsor and only 6 patients were included in the study. The study protocol required concomitant administration of bivalirudin during the active treatment period for controlling the pro-coagulant effects of HepaStem. However, at the time of HepaStem administration the market authorisation for bivalirudin was withdrawn in Poland and the investigator had to stop patients' participation. A third patient was withdrawn before HepaStem infusion on investigator's decision. A PAC was placed in 3 patients, all males, 2 aged below 6 years old and one aged above. The patients were diagnosed with ASDL, ASSL and CPISD. During the active treatment period, one patient (ASSD) had his PAC removed due to SAEs (abdominal pain and device dislocation) just after the first infusion. The other 2 patients received the 4 HepaStem infusions planned in the protocol and were follow-up for 12 months.

Ureagenesis was assessed using the ^{13}C tracer method which was considered as more appropriate compared to ammonia level assessments. Besides, this method was recommended by the PDCO. The BL measures showed a maximum concentration of about 1 µmol/L, reached about 30 minutes after ingestion of the [1-^{13}C] sodium-acetate solution. Similar pattern was observed after HepaStem infusion with for some patients a peak reached about 60 minutes after ingestion. These results were in line with those observed in UCD patients in the HEP001 study which also demonstrate high variability and maximum concentration reached between 30 and 120 minutes after ingestion of the [1-^{13}C] sodium-acetate solution. Median $AUC_{0\text{-}120\ min}$ at baseline ranged between 13.07 and 70.02 min*µmol/L showing high inter- and intra-variability (N = 3, median = 33.39 min*µmol/L patients having received at least one infusion of HepaStem). However, median $AUC_{0\text{-}120\ min}$ seemed to be increased 3 months after HepaStem infusion suggesting a favourable effect of HepaStem infusions (median: 67.995 min*µmol/L; range 61.71; 74.28 min*µmol/L). Again, these results are supportive of those obtained in the HEP001 study who also suggested an increased in the $AUC_{0\text{-}120\ min}$ following HepaStem infusion in UCD patients. In the patient with CPSID, the effect appeared to be maintained throughout the FU period. His protein intake was, as planned in the protocol progressively increased. Biological assessment ammonia and amino acid blood levels were in line with the patient's condition. An episode of non-serious metabolic decompensation occurred at the end of the FU period and triggered the start of an emergency diet. Following HepaStem infusion, the biological and clinical profile of the ASLD patient showed controlled ammonia and amino acid levels as well as a small improvement in the neurological assessment: Ammonia blood levels were high at baseline. They kept fluctuating during the study but tended to decrease and were maintained below 80 µmol/L during the FU period. At the 3-month FU visit, the investigator reported a mild improvement in the patient's neurological status which seemed to persist. However, a neurological decompensation occurred at the end of the FU period. It is known that despite good ammonia control, ASLD patient can experience unremitting intellectual decline and the neurological decompensation observed at the end of the FU period is probably due to the natural course of the disease. Protein intake was increased during the FU period for both patients. However, the intake remained below the BL value and 'WHO safe level'.

Overall, the 3 patients who received at least one infusion of HepaStem reported a total of 72 AEs, mainly during the active treatment period (49 events). The most common events were reported in the 'investigations' (30 events, ASLD and CPSID), infections and infestations (9 events reported by the 3 patients), general disorders and administration site condition (8 events reported by the 3 patients) and metabolism and nutrition disorders (6 events reported by 2 patients) SOC. This is in accordance with the known fragility of the UCD patients who may frequently had abnormal laboratory tests or metabolism disorders and are more vulnerable to infections. Six (6) events were considered as serious, and 2 of them (infusion site pain and device dislocation) led to study discontinuation. A causal relationship with HepaStem was reported for 5 events (infusion site pain [2 events, one serious, the other non-serious], amino acid level increased, pruritus and tachycardia). A causal relationship to concomitant medication related to procedure was considered for 10 events (4 related to tacrolimus and 6 related to bivalirudin). These types of events were commonly reported during the use of these treatments. At the end of the follow-up period, tacrolimus was permanently stopped for both patients who received the full HepaStem infusion.

No deaths, no pregnancies were reported. No particular safety signals were evidenced during vital signs evaluation and physical examination of the patient, or in the immunological tests performed.

In conclusion, the new scheme of HepaStem (4 infusions over a 2-months period) was well tolerated by the 2 patients who received the complete administration scheme. In these 2 patients, ^{13}C test results suggested a positive effect of HepaStem infusion on ureagenesis in UCD patients aged below 12 years old for at least 3 months. One SAE related to HepaStem and catheter placement was considered as serious and led to study discontinuation. No other safety signals were detected. Adverse events and laboratory results were in line with the patient's pathology and guidelines for their management.