SECONDARY SAFETY ENDPOINT – COAGULATION 24 HOURS POST INFUSION

At baseline, most patients (82.6%) had **D-dimer** levels within normal range; 4 patients (17.4%) had non-clinically significant (NCS) baseline D-dimer levels above ULN. All patients presented higher levels of D-dimers within 24 hours post each infusion (compared to prior infusion), except one patient who showed no change or a slight decrease in levels of D-dimers.

Mean baseline level of **fibrinogen** was higher in F3 patients compared to F4 patients (415.5 ± 102.1 mg/dL and 336.1 ± 61.3 mg/dL, respectively). Most patients (82.6%) had baseline fibrinogen levels within normal range.

All F3 patients had baseline **platelet** counts within normal range; while 5 out of 12 F4 patients (41.7%) had NCS platelet counts below LLN.

Most patients had baseline **protein C** and **protein S** levels within normal ranges and presented baseline **INR** and **TT** within normal ranges.

No change was observed in platelet counts, levels of fibrinogen, protein C, protein S, INR, TT within 24 hours post infusion by fibrosis stage, by number of cells administered, or by number of injections.

Most patients (73.9%) had NCS baseline **PAI-1 activity** above ULN; the remaining patients (26.1%) had baseline PAI-1 activity within normal range. A slight decrease in PAI-1 activity was observed within 24 hours post infusion in most patients (-16.2% in 15 out of 23 [65.2%] patients post infusion 1, -26.2% in 8 out of 9 [88.9%] patients post infusion 2, -20.3% in 9 out of 10 [90.0%] patients post infusion 3).

Conclusion on coagulation factors

At baseline, the levels of coagulation factors reflected the exacerbated prothrombotic status in patients with F3 NASH compared to F4 patients (i.e., higher platelet counts and higher levels of fibrinogen and PAI-1 activity). As the liver function declines towards cirrhosis (F4), lowered levels of these parameters and increasing INR were expected.

HepaStem infusion seemed not to have increased the short-term prothrombotic risk in patients with NASH as only transitory increase in D-dimers was reported 24 hours after infusion, which was described for other cell therapies (Moll et al. 2015, Perlee et al. 2018) and for HepaStem in UCD and ACLF patients.

Other coagulation factors, such as platelet counts or levels of fibrinogen, protein C and protein S, were not affected by HepaStem infusion (no change within 24 hours post infusion. Of note, PAI-1 levels slightly decreased 24 hours after infusion.

D-dimer levels returned to pre-infusion values at subsequent time points for all patients except one who presented high D-dimer levels on Day 15 (before the third infusion with HepaStem) which gradually decreased afterwards. Of note, on the day of the first HepaStem infusion, 2 weeks before the peak in D-dimers, the patient reported an AE of local inflammation at the injection site that resolved 6 days after onset.

The values of INR and TT did not change within 24 hours post HepaStem infusion.