Promethera Biosciences SA/NV
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HepaStem: toward an alternative to liver transplantation

Promethera Biosciences' HepaStem platform offers the first allogeneic off-the-shelf, liver-derived stem cell therapy for severe liver diseases that could become an alternative to liver transplantation.

The biopharma company Promethera Biosciences SA/NV is developing the first allogeneic off-the-shelf, liver-derived stem cell therapy for severe liver diseases such as cirrhotic and precirrhotic nonalcoholic steatohepatitis (NASH) and acute-on-chronic liver failure (ACLF). The company provides an end-to-end solution backed by its strong track record in the field of liver diseases, its expertise in manufacturing and building the necessary supply chains to deliver these cell-based therapies to patients in need.

Promethera's development portfolio includes innovative allogenic product candidates derived from ethically donated cadaveric human liver, and the company has two ongoing HepaStem clinical trials: a recently initiated phase 2a study in NASH, and a phase 2a study in ACLF—the first-ever study to use stem cells to treat such indication. The company's patented cell therapy could become an alternative to liver transplantation, a high unmet need given the increased organ shortage worldwide.

The company is looking to upgrade its selected cell candidates together with international industry partners to ensure success in bringing new life-saving drugs to the market.

"HepaStem has a broad therapeutic potential, being a possible first alternative to organ transplant for an ever-growing patient population in dire need, and we are relentless in our drive to bring it to liver disease patients in the safest and fastest way possible," said Etienne Sokal, Promethera's founder and chief scientific and medical officer.

The HepaStem advantage

HepaStem is a highly advanced cell therapy platform consisting of human liver-derived stem cells that are ethically obtained from healthy donors and expanded in a good manufacturing practice (cGMP)-compliant environment. HepaStem cells are administered intravenously, migrate through the bloodstream and accumulate in the liver via the vascular system. In the liver, HepaStem cells exert a number of different effects: 'cooling down' the proinflammatory environment of the diseased liver, inhibiting further hepatic stellate cell activation and slowing down their collagen secretion, thereby reducing fibrosis (**Fig. 1**). This combination of immunomodulatory and antifibrotic paracrine effects provides the mechanistic basis for HepaStem's therapeutic function.

Promethera's HepaStem is a first-in-class biotechnology product for modulating through paracrine effects the immune system and liver fibrosis, which could position it as a viable alternative to liver transplantation for the indications cited above.

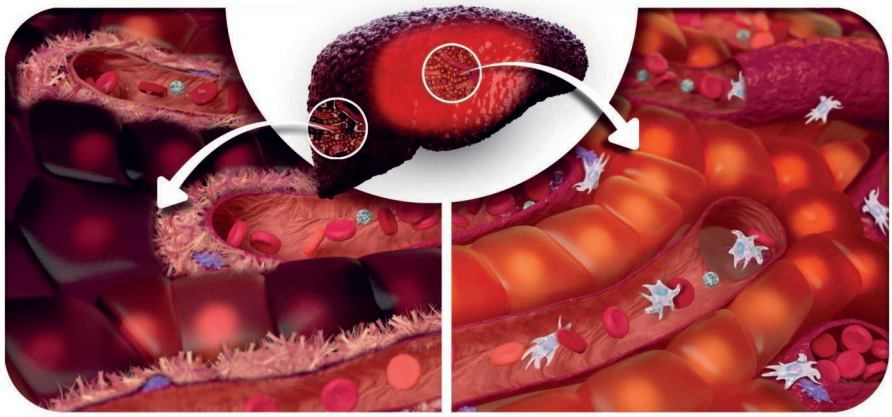

Fig. 1 | Promethera's HepaStem advanced cell therapy platform for severe liver disease. The left image shows hepatic tissue or lobule in a diseased state (fibrotic and inflamed); the right shows the expected state after HepaStem treatment.

Making clinical strides

Promethera has advanced HepaStem into phase 2a clinical studies in both ACLF and late stage NASH.

ACLF is a recently recognized syndrome characterized by acute decompensation (AD) of cirrhosis associated with organ failure. The prevalence of ACLF patients in Europe, the US and Japan is estimated to surpass 70,000 patients annually, for most of whom the prognosis is poor. The only effective cure for patients with ACLF is liver transplantation in association with supportive care before transplantation.

In April 2019, Promethera presented clinical data from an ongoing phase 2a study with HepaStem in patients with ACLF or with AD at a high risk of developing ACLF. This is the first time stem cells have been used to treat ACLF.

No adverse events related to HepaStem occurred at the dosage selected for the trial. In addition to this positive safety profile, the study has already shown positive efficacy trends with improvements in three indicators of liver disease severity evident for up to three months after cell infusion.

NASH is a progressive form of liver disease that carries a risk of progressive fibrosis, cirrhosis and end-stage liver disease. Worldwide, the prevalence of NASH in the general population is 3–5%. In the US, this translates to an estimated >2 million adults with NASH-related, advanced liver disease.

In the second quarter of 2019, Promethera started a phase 2a clinical study of HepaStem in patients with cirrhotic and precirrhotic NASH. The study is expected to be completed in the first half of 2020.

"Moving HepaStem into clinical studies in NASH in addition to the ongoing clinical evaluation in ACLF represents a significant milestone for our therapeutic development activities," said Sokal. "While this first trial in NASH is conducted in Europe and is designed to deliver first clinical results early next year, the clinical development plan for HepaStem is going to expand into the US and Japan in the mid- to long-term."

In addition to setting up clinical development and commercialization partnerships for the above programs, Promethera is looking to advance development candidates from its early-stage cell therapy portfolio together with industry partners and to collaborate with external partners to use Promethera's cell platform to deliver systematically therapeutic candidates of interest.

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