Inotrem announces positive outcome of its Phase II ASTONISH trial in septic shock patients demonstrating efficacy of nangibotide

- *ASTONISH confirms the therapeutic potential of nangibotide in septic shock patients with excessive activation of the TREM-1 pathway*
- *ASTONISH confirms that the soluble TREM-1 biomarker predicts response to nangibotide treatment*

Paris (France), October 13, 2022. Inotrem, an advanced clinical stage biotech company specializing in immunotherapies for acute and chronic inflammatory syndromes, disclosed for the first time today at the International Sepsis Forum held in Barcelona the results for its Phase IIb ASTONISH clinical trial in septic shock patients.

ASTONISH was designed to show the efficacy of nangibotide in septic shock with a precision medicine approach aiming to identify patients who benefit the most from this innovative treatment. This global study enrolled 361 patients across 41 clinical sites in 6 European countries and the United States and succeeded in demonstrating a therapeutic benefit of nangibotide in patients with high levels of the TREM-1 pathway activation marker, soluble TREM-1 (sTREM-1).

ASTONISH studied as a primary endpoint the improvement in SOFA score, a well-established morbidity score evaluating patient clinical evolution and organ function. The change of this score at 5 days after initiation of treatment in the nangibotide-treated arms was compared to the placebo arm in all patients and in patients with a high level of sTREM-1. Importantly, and as part of the prespecified analysis for defining the optimal sTREM-1 cut-off, the benefit of nangibotide high dose treatment versus placebo was clinically and statistically significant at higher concentrations of sTREM-1, representing about 50% of the study population.

Consistent with prior preclinical, observational and Phase IIa trial data in this setting, ASTONISH confirmed that excessive TREM-1 activity is associated with severe immune dysregulation, organ dysfunction and ultimately death.

ASTONISH demonstrates that TREM-1 modulation with nangibotide improves respiratory, cardiovascular and renal function. The study also provided evidence that nangibotide meaningfully impacts other relevant clinical parameters, displaying a trend towards improvement in All-Cause Mortality at day 28 and the proportion of patients Alive and free of organ support at day 28.

Jean-Jacques Garaud, Senior VP Head of scientific and medical affairs at Inotrem, said: *"The ASTONISH trial was designed as a Phase III enabling trial; it generated positive and important insights about nangibotide's therapeutic activity and our precision medicine approach in septic shock. We are enthusiastic about this study and Inotrem's capacity to bring a first in class product in an area with a major unmet medical need".*

"These results represent a major advancement for patients suffering from septic shock. They provide compelling evidence that Inotrem's innovative solution targeting the TREM-1 pathway has the potential to become the first causal treatment for this severe and often fatal indication," said Sven Zimmermann, CEO of Inotrem. *"Based on these data, we intend to advance nangibotide towards*

registration studies in septic shock. We look forward to discussing next steps with regulatory authorities."

Professor Bruno François, Limoges University Hospital and coordinating investigator added: *"We observed that the TREM-1 pathway was activated in severe infections leading to septic shock. Nangibotide is the first TREM-1 inhibitor and ASTONISH confirms its potential as a new therapeutic option for the septic shock patient population. We are looking forward to bringing definitive evidence, in a Phase III clinical study that nangibotide can reduce mortality in these critically ill patients".*

Septic shock is the ultimate complication of sepsis and currently constitutes a high unmet medical need. The incidence of septic shock continuously raises, and mortality remains elevated: it is the 10th leading cause of death in developed countries and the 1st cause of death in intensive care units. There is currently no specific therapy approved for this indication besides antibiotics and symptomatic treatment. Inotrem's solution has the potential to become the first mechanism-based treatment for septic shock.

About nangibotide

Nangibotide is a TREM-1 inhibitor peptide with the potential to restore appropriate inflammatory response, vascular function, and improve post septic shock survival. Nangibotide is the formulation of the active ingredient LR12, which is a 12 amino-acid peptide prepared by chemical synthesis. LR12 is a specific TREM-1 inhibitor, acting as a decoy receptor and interfering in the binding of TREM-1 and its ligand. In preclinical septic shock models, nangibotide was able to restore appropriate inflammatory response, vascular function, and improved animals' survival post septic shock. Nangibotide in septic shock has been granted the fast-track status in September 2019 by the FDA and the PRIME status in 2017 by the EMA. Nangibotide has also been tested in a Phase II trial in severe forms of COVID-19 (ESSENTIAL). ESSENTIAL data will be communicated on October 25. 2022 at the next ESICM meeting in Paris.

About ASTONISH Study

The Efficacy, Safety and Tolerability of nangibotide in Patients with Septic Shock (ASTONISH) phase IIb trial is a Randomized, Double-blind, Placebo Controlled Dose Selection Study that was performed in Europe and in the US. The study compared the effect of nangibotide at two different doses (0.3 and 1mg/kg/h continuous i.v. infusion for 3 to 5 days) versus standard of care.

About Inotrem

Inotrem S.A. is a biotechnology company specialized in immunotherapy for acute and chronic inflammatory syndromes. The company has developed a new concept of immunomodulation that targets the TREM-1 pathway to control unbalanced inflammatory responses. Through its proprietary technology platform, Inotrem has developed the first-in-class TREM-1 inhibitor, nangibotide, with potential applications in a number of therapeutic indications such as septic shock, severe forms of COVID-19 and myocardial infarction. In parallel, Inotrem has also launched an antibody-based program to develop a new therapeutic modality targeting chronic inflammatory diseases. The company was founded in 2013 by Dr Jean-Jacques Garaud, a former head of research and early development at the Roche Group, Prof. Sébastien Gibot and Dr Marc Derive. Inotrem is supported by leading European and North American investors Inotrem is part of the French Tech 120, a government program dedicated to support the development of fast-growing startups. www.inotrem.com

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