Press release
July 12, 2021

Inotrem receives approval to expand nangibotide clinical trial in critically ill COVID-19 patients and receive additional public funding of €45 million

- **Inotrem's phase 2/3 clinical trial "ESSENTIAL" will enroll up to 730 patients in Europe to demonstrate the safety and efficacy of nangibotide to treat critically ill COVID-19 patients with respiratory failure.**

- **Recent preclinical studies have strengthened the body of evidence for targeting the TREM-1 pathway which is activated in a subset of patients suffering from severe COVID-19.**

Paris, July 12, 2021. Inotrem S.A., a biotechnology company specializing in the development of immunotherapies targeting the TREM-1 pathway, announces that it has obtained authorization to pursue the clinical development of nangibotide up to registration in COVID-19 patients from both the French and Belgian competent authorities.

As part of this program, Inotrem receives additional 45 million euros in public funding under the "Capacity Building" Call for Expression of Interest, operated on behalf of the French government by Bpifrance, the French national investment bank, as part of the *Programme d'investissements d'avenir (PIA)* and the France Recovery Plan, bringing French state support for the project to a total of 52,5 million euros. This public funding will support Inotrem's clinical program including the phase 2/3 study "ESSENTIAL" which aims to demonstrate the efficacy and safety of nangibotide in treating patients in respiratory distress with severe forms of COVID-19.

The primary endpoint is evaluation of the impact of nangibotide on the progression of disease in patients receiving ventilatory support due to COVID-19 as well as on the severity of the respiratory failure, duration of mechanical ventilation, length of stay in intensive care and mortality. In "ESSENTIAL", a Phase 2/3 clinical program, up to 730 patients will be enrolled initially in France and Belgium and, possibly in other European countries. Pre-defined interim analyses will be conducted by an independent Data Monitoring Board to test futility and to allow for the study design to be adapted as necessary. "ESSNTIAL" is the continuation of a 60 patients phase 2a evaluating the safety and efficacy of nangibotide in patients suffering from severe COVID-19. In July 2020, the CoviTREM-1 consortium, which includes the Nancy and Limoges university hospitals and Inotrem, obtained public funding of 7,5 million euros under the "PSPC-COVID" call for projects, operated on behalf of the French government by Bpifrance

New pre-clinical studies with nangibotide have demonstrated that the administration of nangibotide in murine models infected with SARS-CoV-2 was associated with a decrease in inflammatory mediators and an improvement of clinical signs, in particular respiratory function, and survival. Inotrem also confirmed in 3 different and independent cohorts that sTREM-1, a marker of the activation of the TREM-1 biological pathway, is associated with both severity and mortality in critically ill COVID-19 patients.

Leveraging the results of these preclinical studies and the implications for the role of the TREM-1 pathway in COVID-19, Inotrem has filed additional patents to cover nangibotide use in severe forms of COVID-19 as well as the use of sTREM-1 as a biomarker and companion diagnostic. This significantly strengthens Inotrem's already broad patent estate.

Jean-Jacques Garaud, Executive Vice-President, Head of Scientific and Medical Affairs and Inotrem's co-founder said :*"We are eager to pursue the development of nangibotide in these severe forms of COVID-19. Nangibotide is a TREM-1 inhibitor which has already demonstrated a trend towards efficacy in septic shock patients and has the potential to modulate the dysregulated immune response in critically ill COVID-19 patients. With this large clinical study, we can demonstrate efficacy for nangibotide in a further indication with the goals of reducing the duration of hospitalization and mortality."*

Sven Zimmerman, CEO of Inotrem, also declared: "*The size of the financial support awarded to us as part of the French government's initiative against COVID-19 is a testimony to the relevance of targeting the TREM-1 pathway with nangibotide in these severely ill patients. We are delighted by the confidence placed in our technology and our team. Everyone at Inotrem is fully committed to deliver on this ambitious program alongside nangibotide's ongoing Phase 2b trial in septic shock patients."*

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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, LR12 (nangibotide), with potential applications in a number of therapeutic indications such as septic shock and myocardial infarction. In parallel, Inotrem has also launched another 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.
www.inotrem.com

About TREM-1 pathway
TREM-1 pathway is an amplification loop of the immune response that triggers an exuberant and hyperactivated immune state which is known to play a crucial role in the pathophysiology of septic shock and acute myocardial infarction.

About Nangibotide
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.

About ESSENTIAL study:
The Efficacy and Safety Study Exploring Nangibotide Treatment in COVID-19 pAtients with ventiLatory support, is a randomized, double-blind, placebo-controlled confirmatory study with adaptive features that will be performed in Europe. This is a pivotal study and it is expected that based on its results, nangibotide could be registered in this indication. The first part of the study (i.e.: 60 patients) has been already finalized and assessed by an independent data monitoring committee with excellent safety results. The study will recruit up to 730 patients in up to 40 sites. Several interim and futility analyses are foreseen as part of the adaptive design of the study.

About Bpifrance
Bpifrance is the French national investment bank: it finances businesses – at every stage of their development – through loans, guarantees, equity investments and export insurances. Bpifrance also provides extra-financial services (training, consultancy.). to help entrepreneurs meet their challenges (innovation, export…).
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