PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Rationale and protocol for the Efficacy, Safety and Tolerability of Nangibotide in Patients with Septic Shock (ASTONISH) Phase IIb randomised controlled trial
AUTHORS	Francois, Bruno; Lambden, Simon; Gibot, Sebastien; Derive, Marc; Olivier, Aurelie; Cuvier, Valerie; Witte, Stephan; Grouin, Jean-Marie; Garaud, Jean Jacques; Salcedo-Magguilli, Margarita; Levy, Mitchell; Laterre, Pierre-François

VERSION 1 – REVIEW

REVIEWER	Hongcai Shang Dongzhimen Hospital, Beijing University of Chinese Medicine
REVIEW RETURNED	20-Oct-2020

GENERAL COMMENTS	1. In the part of Strengths and Limitations of the study, the authors mentioned acute morbidity. Please provide details in the manuscript. 2. In the table 1, the inclusion criteria include patients with 18-85 years old and Documented or suspected infection: lung, abdominal or urinary tract infection (UTI) in the elderly (≥65 years). If the patients have to meet all of the inclusion criteria, the patients' age should be 65-85. 3. Please provide details of recruitment 4. Please provide details/definitions of some outcomes, such as immune and vascular related biomarkers, renal support, hematology, coagulation, plasma biochemistry. 5. Please discuss the limitations of the study design.

REVIEWER	Barak Pertzov Rabin Medical Center, Israel
REVIEW RETURNED	21-Oct-2020

GENERAL COMMENTS	Dr. Francois and colleagues have submitted a protocol for a study that will evaluate the safety and efficacy of the novel drug Nangibotide that attenuates the TREM-1 pathway in sepsis. This is a large multicenter randomized study that will take place in several countries. The introduction is well written and informative. Blinding, allocation concealment, inclusion and exclusion criteria, outcomes and statistical analysis are well described in the protocol. I congratulate the authors for their excellent work and wish them good luck in conducting this study

	Minor revisions: 1. Planned Study initiation dates are not specified 2. Line 137 should be corrected

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author
1. In the part of Strengths and Limitations of the study, the authors mentioned acute morbidity. Please provide details in the manuscript.

We thank the reviewer for this comment. The acute morbidity is characterised by the primary outcome of the study, the change in SOFA score. We clarify this in the discussion:

Change in SOFA, an established marker of the acute morbidity associated with sepsis, has been consistently shown to act as a surrogate for subsequent mortality in septic shock[27]

2. In the table 1, the inclusion criteria include patients with 18-85 years old and Documented or suspected infection: lung, abdominal or urinary tract infection (UTI) in the elderly (≥65 years). If the patients have to meet all of the inclusion criteria, the patients' age should be 65-85.

We thank the reviewer for the opportunity to clarify. IN this study, all patient with lung or abdominal source of sepsis are eligible within the age range 18-85. Patients with UTI are only eligible if they are 65-85. We have revised the text of table 1 accordingly:

Documented or suspected infection: lung, abdominal or, in patients aged ≥65 years, urinary tract infection (UTI).

3. Please provide details of recruitment

We have added the following text to the randomisation section:

Following screening for eligibility, study centres will contact a central, independent coordinating centre to confirm eligibility. They will then be issued with a unique randomization code that will facilitate identification of the correct blinded allocation of study drug.

4. Please provide details/definitions of some outcomes, such as immune and vascular related biomarkers, renal support, hematology, coagulation, plasma biochemistry.

We are pleased to provide as supplementary text a detailed summary of the investigations listed and the time points at which they will be collected.

5. Please discuss the limitations of the study design.

We have added the following paragraph to our discussion:

Limitations of this phase IIb study include the use of a surrogate endpoint to detect clinically relevant efficacy. Whilst the change in SOFA score has been extensively validated, further studies will be required to demonstrate improved mortality as a primary outcome. Furthermore, by defining *a priori* the subgroup of patients with elevated sTREM-1 levels as those most likely to benefit, the available statistical power to detect a benefit only in those patients with low sTREM-1 levels at baseline is reduced.

Reviewer: 2

Comments to the Author
Dr. Francois and colleagues have submitted a protocol for a study that will evaluate the safety and efficacy of the novel drug Nangibotide that attenuates the TREM-1 pathway in sepsis. This is a large multicenter randomized study that will take place in several countries. The introduction is well written and informative. Blinding, allocation concealment, inclusion and exclusion criteria, outcomes and statistical analysis are well described in the protocol.
I congratulate the authors for their excellent work and wish them good luck in conducting this study

Minor revisions:
1. Planned Study initiation dates are not specified

We have added the following sentence: The study was initiated in November 2019

2. Line 137 should be corrected

We have removed this sentence.

Reviewer: 1
Competing interests 1: None declared.

Reviewer: 2
Competing interests 1: None