DATA MONITORING COMMITTEE (DMC) CHARter

MOT-C-203

Efficacy, Safety and Tolerability of Nangibotide in Patients with Septic Shock.
A Randomized, Double-blind, Placebo Controlled Dose Selection Study

Test Product: Nangibotide

Sponsor: INOTREM S.A.
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Sponsor Protocol Number: MOT-C-203

EudraCT Number: 2018-004827-36
pIND: 131824

Development Phase: IIb

DMC Chair: Michel Wolff, MD

Version: 2.0
Date: 10 October 2019

Confidential

Information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical/regulatory review of the study, without written authorisation from INOTREM SA or its affiliates.
5 PREAMBLE

An independent data monitoring committee (DMC) will be appointed to guide dose selection and to monitor the safety of study MOT-C-203 “Efficacy, Safety and Tolerability of Nangibotide in Patients with Septic Shock. A Randomized, Double-blind, Placebo Controlled Dose Selection Study”

6 MEMBERS

The DMC will comprise experts with experience in the treatment of sepsis and septic shock and the conduct of clinical trials in this indication. It will consist of 4 members including 3 specialists in intensive care medicine and management of patients with septic shock, and a methodologist (biostatistician) with experience in the conduct and the safety assessment of clinical trials. All four are voting members. The chair of the DMC will be appointed by the sponsor, INOTREM. Other DMC members and back-ups will be mutually agreed between the sponsor and the DMC chair. The DMC members should be free of financial or scientific conflicts of interest and are responsible for advising the Sponsor of any changes in interests that would affect their objectivity. All DMC members will provide a signed CV and financial disclosure forms to the sponsor prior to the constitution of the DMC.

The current list of members and their contact information is provided in appendix 1.

7 RESPONSIBILITIES

The DMC will be responsible for:

- Reviewing safety data from an unblinded interim analysis after 112 (25%) randomized patients completed day 7
- Reviewing safety and efficacy data from an unblinded interim analysis after 225 (50%) randomized patients completed day 7 and making a recommendation for the study or a treatment arm to stop in case of futility or making a recommendation for the increase of sample size
- Reviewing SAEs and other safety data on an ongoing basis
- Reviewing the general progress of the clinical study with regard to accrual/withdrawals or drop-out rates and clinical study conduct

In addition to the review of unblinded safety data at 25% and safety and efficacy data at 50% of patients treated, DMC members may have access to unblinded safety data for one or more patients where necessary. However, no members of the study team at INOTREM, at the Contract Research Organization (CRO) or the sites) will have access to unblinded data until after database lock is declared. In case unblinded data needs to be handled or analyzed before database lock, these tasks will be performed by persons independent from the study team.

8 DMC MEETINGS

8.1 Meeting Schedule

DMC meetings will be held at the following timepoints:

- Initial Meetings for the set-up of the DMC and its procedures (e.g. charter, analysis plans)
- Unblinded meetings for the assessment of interim analyses
- Additional or unscheduled meetings
8.2 Format and Scheduling of Meetings

The preferred meeting format will be face-to-face meetings held at INOTREM’s offices in Paris. However, meetings in the format of a teleconference with single or all participants calling by phone may be conducted, depending on the availability of the person. The meeting will consist of an open and a closed part. During the open part, the sponsor will present available data and provide responses to questions. During the subsequent closed part, only the DMC members will discuss the data and decide on recommendations to the sponsor. The closed session discussions are confidential.

The meetings will be scheduled by the DMC chair in cooperation with the sponsor. Effort should be made to keep the timelines between the data lock point and the DMC recommendations as short as possible. The sponsor will communicate the current study status on a regular basis and agree timelines with the DMC for their review in advance.

The content of the DMC briefing packages will be agreed between the sponsor and the DMC chair and may be adjusted during the course of the study. This will be documented in a separate document "DMC Statistical Analysis Plan".

The summary data reports will be provided to the DMC members prior to the scheduled meeting. Due to the nature of the study, these may be available only on a short notice. Efforts will be made to provide these at least 24 hours prior to the meeting. INOTREM will liaise with the DMC chair to ensure availability of the DMC members for review.

8.3 Initial DMC Meetings

The first meetings of the DMC will be organizational meetings. They will be held during the final stage of study set-up, to provide advisory review of the scientific and ethical issues relating to the study design and conduct, to discuss the standard operating procedures for the role and functioning of the DMC, and to discuss the format of reports that will be used to present trial data at future DMC meetings.

8.4 Unblinded DMC Meetings for the Assessment of Interim Analyses

Unblinded DMC meetings for the assessment of interim analyses are scheduled at the following timepoints:

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>25% of patients treated (i.e. 112 patients completing D7)</td>
<td>Safety</td>
</tr>
<tr>
<td>50% of patients treated (i.e. 225 patients completing D7)</td>
<td>Safety; Efficacy: assessing the study or a treatment arm for futility</td>
</tr>
</tbody>
</table>

8.4.1 Interim Assessments of Safety

After the completion of day 7 of the last patient of the respective review point, the sponsor will provide a report with cumulative safety and PK data (as available) for the DMC to review. The «data lockpoints» is defined as day 7 of the last patient for the respective timepoint.
The following data will be required:

<table>
<thead>
<tr>
<th>Data</th>
<th>Description/Format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Adverse Events</td>
<td>All SAE data as line listing and CIOMS forms (blinded)</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>Tabular report of <strong>all adverse events</strong>, available in the eCRF system 24 hours</td>
</tr>
<tr>
<td></td>
<td>after the data lock point. Sites should make effort to complete data entry for</td>
</tr>
<tr>
<td></td>
<td>safety data for all patients until then.</td>
</tr>
<tr>
<td>Demographics and Vital</td>
<td>• Demographics data listing</td>
</tr>
<tr>
<td>Signs</td>
<td>• Blood Pressure data listing</td>
</tr>
<tr>
<td></td>
<td>• Body temperature data listing</td>
</tr>
<tr>
<td>Clinical Laboratory</td>
<td>Tabular report of the parameters available in the eCRF system:</td>
</tr>
<tr>
<td></td>
<td>• <strong>Chemistry:</strong> Aspartate aminotransferase, Alanine aminotransferase,</td>
</tr>
<tr>
<td></td>
<td>total bilirubin, creatinine, urea, glucose, sodium, potassium, chloride,</td>
</tr>
<tr>
<td></td>
<td>calcium, inorganic phosphate, total protein, albumin, lactate</td>
</tr>
<tr>
<td></td>
<td>• <strong>Haematology:</strong> Hemoglobin, hematocrit, leucocytes, basophils,</td>
</tr>
<tr>
<td></td>
<td>eosinophils, neutrophils, lymphocytes, monocytes, platelet count</td>
</tr>
<tr>
<td></td>
<td>• <strong>Coagulation:</strong> International Normalized Ratio (INR), disseminated</td>
</tr>
<tr>
<td></td>
<td>intravascular coagulation (DIC) score</td>
</tr>
<tr>
<td></td>
<td>• Pregnancy test.</td>
</tr>
<tr>
<td>ECG</td>
<td>ECG Data listing</td>
</tr>
<tr>
<td>Patient narratives</td>
<td>Narratives (discharge letters) of for all patients</td>
</tr>
<tr>
<td>PK data</td>
<td>PK data will be provided to the extent available at the respective datalock point</td>
</tr>
</tbody>
</table>

Details on the briefing documentation such as tables, listings and figures will be defined in the DMC statistical analysis plan (Appendix 2).

### 8.4.2 Interim Assessments of Efficacy (Futility)

The interim analysis after 225 patients will also include an assessment of efficacy for deciding on whether one treatment arm or the entire study should be stopped for futility.

The assessment of futility will be made primarily on the basis of the primary endpoint (change in SOFA score). The recommendation should be based on the "standardized effect", which is defined as the difference in LSMEANS (placebo - dose) in the ANCOVA model for the analysis of the primary endpoint divided by the residual standard deviation. Hence a positive standardized effect favors the nangibotide dose and vice versa.

Nevertheless, the clinical endpoint all-cause-mortality after day 28 should also be taken into consideration. The difference in mortality rates (placebo - dose) will also be provided. A positive estimated difference in mortality rates favors the nangibotide dose and vice versa.

Details on the briefing documentation such as tables, listings and figures will be defined in the DMC statistical analysis plan (Appendix 2).

For the assessment of futility, each dose should be assessed separately.
Rules to claim a dose futile are defined below:

- IF the standardized effect is $< +15\%$ in both populations (i.e. all comers and subgroup with high sTREM-1 levels, G2)

AND

- the difference in mortality rates is $< +5\%$ in both populations (i.e. all comers and subgroup with high sTREM-1 levels, G2)

$\Rightarrow$ the dose is considered futile

In addition:

If there is a major safety issue with the dose (risk-benefit no longer acceptable), the treatment arm should be considered futile.

A description of the process for deciding on the futility of one dose is provided in Figure 1, a summary of the futility decisions is provided in Figure 2.

![Decision Tree for Assessing Futility of a Treatment Arm](image1)

**Figure 1: Decision Tree for Assessing Futility of a Treatment Arm**

- Both doses futile or unsafe $\Rightarrow$ Trial on hold
- One dose non futile and safe $\Rightarrow$ Continue study with this dose
- Both doses non futile and safe $\Rightarrow$ Continue study with both doses

![Decision Tree for Futility Decisions](image2)

**Figure 2: Decision Tree for Futility Decisions**
For the assessment of futility, it should be taken into account, that the dataset on D28 mortality is limited on sample size and may even be not complete. A decision to stop a treatment arm or the study for futility on grounds of mortality should be confirmed with complete D28 mortality data.

Further details will be defined in the DMC statistical analysis plan (Appendix 2).

### 8.4.3 Additional DMC Meetings

Additional meetings of the DMC can be scheduled by the DMC chair or the sponsor as deemed necessary for the assessment and discussion of safety aspects.

### 8.5 DMC Recommendations

The DMC recommendations after each DMC meeting will include one of the following:

- Continuation of the study without modifications
- Continuation of the study with modifications. The recommended modifications may be within or beyond the adaptive feature of the study protocol (study protocol section 8.2).
- Request for additional information
- Suspension of the study (put study “on-hold”) on grounds of safety for consultation with regulatory authorities
- Discontinuation of the study on grounds of safety

For the DMC meeting after 225 patients, the DMC recommendation will include one of the following:

- Discontinuation of study on grounds of futility or safety
- Discontinuation of one treatment arm on grounds of futility or safety

The DMC chair will communicate their recommendation to the sponsor immediately after the end of the closed part of the DMC session orally or by phone followed by an email.

### 8.6 Meeting Minutes

The DMC will prepare closed minutes of their meeting. The minutes will be signed by all DMC members and originals kept by the Chairperson until unblinding of the study. Following each meeting, summary minutes will be drafted and distributed within 2 business days by the Chairperson to the other DMC members. The minutes will be reviewed and approved by the DMC members within 5 business days of distribution and signed by the chair of the DMC. The Final minutes will be kept securely by the DMC chair and transferred to the sponsor after database lock.

### 8.7 Records Retention

The DMC Chair will retain copies of all meeting minutes, notes, copies of safety reports and findings, vote results, recommendations and reports used in the evaluation of safety of protocol until database lock is declared by the sponsor, at which time the materials will be transferred to the Sponsor.

### 9 REPORTING OF STUDY PROGRESS AND IMPORTANT EVENTS TO DMC

The sponsor will report the progress of the study to the DMC members on a regular basis. The following important events will be reported to the DMC immediately:

- Serious Adverse Event with the outcome «death»
10 COMMUNICATION POLICY

It is the responsibility of the Sponsor to communicate with the sites and ethics committees (where required) on a regular basis. The initial communication will include a copy of this charter and previous DMC recommendations.

11 ACCEPTANCE OF DMC RECOMMENDATIONS

It should be understood that the DMC represents an advisory body for the Sponsor. While it is unlikely that the sponsor would ignore DMC recommendations, the company is not obliged to follow DMC recommendations. Thus, upon receiving a DMC recommendation, the Sponsor will decide upon appropriate potential steps in consultation with the DMC, and and/or relevant regulatory authorities, as required. It is understood that the Sponsor can elect to continue, interrupt, or close the study even if the DMC were to recommend a different course of action.

If the DMC recommends study interruption/termination, the Sponsor may also request consultation from relevant regulatory authorities.

Once a DMC recommendation to stop the study is accepted, the Sponsor will be responsible for notifying regulatory agencies, investigators, and ethics committees of the DMC’s recommendations and the company’s decision to stop the study. These activities will be performed consistent with GCP guidelines and relevant regulatory requirements.

If the DMC recommends that the trial be stopped, but the Sponsor decides to continue the trial, the Sponsor will provide a written explanation of the decision to the DMC within 14 business days. If a DMC recommendation to stop the study is rejected by the Sponsor, the company will be responsible for notifying regulatory agencies, investigators and ethics committees of the DMC’s recommendations and the company’s decision to continue the study. These activities will be performed consistent with GCP guidelines and relevant regulatory requirements.

The Sponsor or the investigators are at liberty to interrupt or close the study at one or more sites without consulting the DMC. However, it is expected that the DMC would be notified of such actions.