Algemene gegevens / General Information

Programma / Programme	:	**COVID-19 Programma**
Subsidieronde / Subsidy round	:	**Bottom-up ronde COVID-19 aandachtsgebied 1**
Projecttitel / Project title	:	**Open-label phase I/IIa study to assess safety and efficacy of low anticoagulant heparin in COVID-19**
Projecttaal / Project language	:	**Engels / English**
Geplande startdatum / Planned start date	:	**15-07-2020**
Geplande duur / Planned duration	:	**12 maanden / months**
Datum indienen / Date of application	:	**14-05-2020**
Projecttype / Project type	:	**Toegepast onderzoek**
Vervolg eerder ZonMw-project / Continuation previously funded project ZonMw	:	**Nee / No**

Projectleden / Project members

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Projectgegevens / Project information

Aandachtsgebieden / Focus

1.1 Thema's aandachtsgebied 1
- Behandeling

1.3 Setting
- Ziekenhuiszorg

Samenvatting / Summary

Pathogenesis underlying COVID-19 progressing to severe and critical disease remains poorly understood and, consequently, there is a lack of adequate therapy.
We hypothesized that activated neutrophils and their downstream effects play a central role in microvascular injury, activated platelets and the procoagulant state that is so characteristic in these patients. Having this in mind we started a METC-approved biomarker study in COVID-19 patients as soon as it became apparent that the corona crisis would hit the Netherlands with unprecedented severity. We included patients of whom serum and plasma samples were collected at base line (presentation at the hospital for triage because of suspected COVID-19, proven by typical radiological findings on CT-scan, and confirmed by rt-PCR), and during follow up in case patients were hospitalized. We differentiated between mild, moderate, progressive and severe disease.
Preliminary analysis supports our hypothesis since neutrophils are increasingly activated in the progressive and severe patients. This is indicated by NETosis, with subsequent release of nuclear histones, activated platelets, and activation of both the coagulation cascade and the vessel wall. Of note, the level of extracellular histones predicts disease severity and mortality in these patients. Extracellular histones are recognised as mediators of death in various diseases and neutralisation of these histones increases survival from sepsis.
Negatively charged heparins neutralize extracellular histones. For this purpose, we designed the low anticoagulant heparin M6229 that neutralizes extracellular histones and that can be administered at high dose without bleeding risk. M6229 is currently being developed by Matisse Pharmaceuticals as a new investigational drug to treat patients with sepsis. This project aims to test the benefit of M6229 therapy for COVID-19 patients in a phase I/IIa pragmatic controlled open-label and proof-of-concept study.

Trefwoorden / Keywords

COVID-19, Treatment, Extracellular Histones, Low anticoagulant heparin

Samenwerking / Collaboration

Samenwerking tussen onderzoek en praktijk / Cooperation between research and practice:

Ja / Yes

Organisaties

Matisse Pharmaceuticals

Inhoud / Content

Disciplines / Disciplines

- Infecties, parasitologie, virologie / Infections, parasitology, virology
- Geneeskunde, overig / Medicine, other
- Immunologie, serologie / Immunology, serology
- Biochemie / Biochemistry

Financiële gegevens / Financial data

ZonMw budget

	Jaar / Year								
Kostenpost	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	**Totaal / Total**
Personeel	5.1.1c								
Materieel									
Implementatie									
Apparatuur									
Overig									
Totaal / Total									

Co-financiering / Cofinancing

Naam co-financier / Name of cofinancier	Bedrag / Amount	Status

Bijzondere gegevens / Additional information

Vergunningen / Permits

	Verklaring nodig / Statement required?		Status verklaring / Statement status		
	Ja / Yes	Nee / No	Verkregen / Acquired	Aangevraagd / Applied	Nog niet aangevraagd / Not applied yet
METC	X				X
DEC		X			
WBO		X			

Onderschrijvingen / Assents

	Ja / Yes	Nee / No	N.v.t. / N.A.
Code biosecurity / Code Biosecurity			X
Code openheid dierproeven / Code Transparency of Animal Testing			X

Andere vergunningen / Other permits

AANVRAAGFORMULIER PROJECTIDEE – BOTTOM-UP RONDE

COVID 19 programma

Deadline voor indiening: 14 mei 2020 (14:00 u)

LEES ALSTUBLIEFT ALLE INSTRUCTIES IN BIJLAGE ''TOELICHTING INDIENING PROJECTIDEE'' VAN DE OPROEPTEKST ZORGVULDIG!

Wanneer u het formulier heeft ingevuld:

1. **Zet het formulier om naar een PDF file en controleer de details**
2. **Upload het complete formulier als een bijlage bij uw indiening in Projectnet (Let op: dit zijn twee verschillende links, gebruik maar 1 van de 2!)**

ProjectNet: Aandachtsgebied 1 (voorspellende diagnostiek en behandeling)
ProjectNet: Aandachtsgebied 2 (zorg en preventie)

BASISGEGEVENS (voorpagina)

NAAM VAN DE HOOFDAANVRAGER:

5.1.2e 5.1.2e

ORGANISATIE:

MUMC

PROJECTTITEL:

Open-label phase I/IIa study to assess safety and efficacy of low anticoagulant heparin in COVID-19

DATASTEWARD:

Wie is de datasteward die de open science en FAIR data planning in uw project ondersteunt? Zie de webinars op de ZonMw website om de datastewards te informeren en ondersteunen.

☒ Ik betrek een datasteward bij mijn project:
Naam: Nog niet bekend
Instituut: Klik of tik om tekst in te voeren.
E-mail: Klik of tik om tekst in te voeren.
Was aanwezig bij de webinar: ☐ Ja ☒ Nee

☐ Ik heb nog geen datasteward.

ONDERZOEKSVOORSTEL **max 3 pagina's A4** (inclusief literatuurreferenties)	(voorpagina met basisgegevens niet meegerekend - font type Arial 10 pts)

1. PROBLEEMSTELLING EN DOELSTELLING(EN):

SARS-CoV-2 causes disease with symptoms that can vary from mild respiratory complaints to severe lung injury, systemic inflammation, thrombophilia and multi-organ failure. Patients with mild symptoms can fully recover or rapidly progress towards severe and critical disease with high risk of mortality. The pathogenesis underlying disease progression remains poorly understood and, consequently, there is a lack of adequate therapy.

One can distinguish separate domains referring to different targets of therapy. Examples are antiviral therapy, immunomodulation, and anticoagulation. The goal of therapy is to improve survival, shorten hospital stay, but also to prevent the long term sequelae and morbidity of COVID-19.

We hypothesized that activated neutrophils and their downstream effects play a central role in the microvascular injury, the activated platelets and the procoagulant state that is so characteristic in these patients. Having this in mind we started a METC-approved biomarker study in COVID-19 patients as soon as it became apparent that the corona crisis would hit the Netherlands with unprecedented severity. To date we included 250 patients of whom serum and plasma samples were collected at base line (presentation at the hospital for triage because of suspected COVID-19, proven by typical radiological findings on CT-scan, and confirmed by rt-PCR), and during follow up in case patients were hospitalized. We differentiated between mild, moderate, progressive and severe disease.

Preliminary analysis supports our hypothesis since neutrophils are increasingly activated in the progressive and severe patients. This is indicated by elevated base line C5a levels, the formation of neutrophil extracellular traps (NETosis), with subsequent release of nuclear histones, activated platelets, and activation of both the coagulation cascade and the vessel wall (1,2). Of note, the level of extracellular histones predicts disease severity mortality of these patients (manuscript in preparation). Extracellular histones are recognised as mediators of death in various diseases including sepsis and neutralization of extracellular histones increases survival from sepsis (3).

Negatively charged heparins neutralize extracellular histones. For this purpose, we designed the low anticoagulant heparin M6229 that neutralizes extracellular histones and that can be administered at high dose without bleeding risk and that reduces mortality in various animal models of sepsis (4). M6229 is currently being developed by Matisse Pharmaceuticals as a new investigational drug to treat patients with sepsis.

This project aims to test the benefit of M6229 therapy for COVID-19 patients in a phase I/IIa pragmatic controlled open-label and proof-of-concept study and to explore the relevance of this new domain, and novel target of treatment so it could be added to the REMAP-CAP platform.

2. PLAN VAN AANPAK:

The work plan has 3 work packages.

Work Package 1 (WP1): Regulatory preparation for a phase I/IIa open-label, proof-of-concept trial

Lead: Matisse Pharmaceuticals. Contributors: Maastricht UMC+

The clinical trial will assess safety and therapeutic effect of investigational drug M6299 (a low anticoagulant heparin) in COVID-19 patients. WP1 will prepare a full compulsory research file for review by the Central Committee on Research Involving Human Subjects (CCMO), including:

- Research protocol
- General assessment and trial registration (ABR form)
- Investigator Brochure (IB) providing a summary of available preclinical data
- Investigational Medicinal Product Dossier (IMPD) providing data on production and quality
- Hospital pharmacist product details & product labelling for M6229
- Applicable statements and licenses regarding production and storage of M6229
- Information leaflet and consent form for trial participants
- Clinical trial agreement & contracts

We aim to include 30 proven COVID-19 patients at Medium Care Unit or shortly after admission at ICU (within 48 hours). We fully acknowledge the vulnerability of COVID-19 patients (and their relatives) as well as the fact that recruitment of study participants will take place at a time that is full of emotional stress.

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Work Package 2 (WP2): Execution of the phase I/IIa trial.

Study sponsor: Maastricht UMC+. Recruiting centers: Maastricht UMC+. Administrative support: Matisse Pharmaceuticals. Other UMC sites are optional depending on inclusion rate.

The study aims to enrol 30 patients over a 3-6 months inclusion period. Primary inclusion

criteria include proven SARS-CoV-2 infection, positive CT scan and moderate to severe clinical features. Major exclusion criteria include history of heparin-induced thrombocytopenia. The study has two objectives:
1) First phase to assess safety, tolerability and in case feasible also PK of intravenously administered M6229.
2) Second phase to demonstrate proof-of-concept of M6229 therapy on top of standard of care. To this end, the trial will entail an open-label administration with the established highest tolerated dose.
The study will start with administration of M6229 at an infusion rate of 0.15 mg/kg/h for a period of 24 hours in 3 patients. This is equivalent to commonly used therapeutic doses of unfractionated heparin (UFH). Provided that no safety issues arise, subsequent groups of 3 patients will be recruited to receive the drug at escalating doses of 0.5, 1.5 and 3 mg/kg/h. The highest tolerated dose will be determined based on the absence of relevant safety issues. The second phase will enrol 12 patients who will receive the highest tolerated M6229 dose on top of standard of care and 12 patients who wil receive standard of care.
Safety and tolerability will be assessed continuously throughout the infusion period and until 24 hours thereafter, and will specifically focus on platelet counts, bleeding complications, hypersensitivity reactions and aminotransferase (ASAT, ALAT) levels. Tolerability and safety will be monitored by responsible investigators.
PK data will be collected at selected time points in order to determine volume of distribution, C max, steady-state plasma concentration, clearance, and elimination half-life. Finally, to assess preliminary efficacy of M6229 treatment we will measure progression of disease, extracellular histones, coagulation parameters and elected biomarkers including C5a

Work package 3 (WP3): Biomarker analysis. WP3 will collect serum and plasma samples from included patients at baseline and at consecutive time points during the study. Following biomarkers will be measured in plasma samples: extracellular histone 3, complement C5a, thrombin-antithrombin (AT) complex, VIIa-AT complex, IXa-AT complex, XIa-AT complex, XIa-α1anti-trypsin complex and kallikrein. The effect of serum samples on endothelial cell viability and NETosis will be measured using human microvascular endothelial cells (HMEC-cell line) and neutrophils from healthy volunteers, respectively.

3. HAALBAARHEID VAN HET PROJECT:

TIJDSSCHEMA
The project period is from 15 July 2020 to 30 June 2021. From the start we foresee a period of 2 months to complete the standard research file for the Phase I/IIa trial and to obtain approval from the METC. As preparation for patient enrolment will take place simultaneously, we expect to initiate the fase I/IIa trial in September/October 2020. Inclusion of the patients is expected to take 2-3 months depending on the intensity of the second wave of corona infections. Estimated study completion is March 2021 and data analysis is expected to be finalized in June 2021. The study results will be analyzed and published under full academic responsibility of the study PIs.

MOTIVATIE HAALBAARHEID
The aims of the study will be achieved within the outlined time frame because a second wave of infections is highly likely to occur in the second half of this year. The intensity, however, cannot be predicted with accuracy. During the first wave MUMC+ enrolled 15 COVID-19 patients in the PANAMO study in 10 days. We expect that within 3 months all patients will be recruited. Matisse Pharmaceuticals is currently in the process of building a common technical dossier for the phase I/IIa clinical trial application and is conducting a toxicology study in primates with an expected completion at the end of June 2020. M6229 is obtained from UFH after separation based on affinity binding to antithrombin using a GMP grade process established by Matisse Pharmaceuticals. Production process including fill&finish are operative. M6229 has been shown to neutralise histone cytotoxicity in vitro and to improve survival in non-clinical animal models of sepsis in vivo.

4. RELEVANTIE VOOR DE PRAKTIJK:

Onderbouw de relevantie aan de hand van de in de subsidieoproep benoemde relevantiecriteria
1 The project aims to deliver a therapy to treat COVID-19 patients. The concept of the therapy is based on an overwhelming host response and, hence, will be applicable to other viral infections causing pneumonia.
2 The concept of the treatment was conceived at Maastricht University.
3 To the best of our knowledge, this project is worldwide the first in its kind to obtain proof-of-concept in COVID-19 patients.
4 Matisse Pharmaceuticals (MP) will provide IMPD and medication. Costs for patient management, data monitoring and biomarker analyses are requested.

5 The results of this project will be used to broaden our understanding of the host response to coronavirus infection and to design clinical Phase II and III trials.
6 If successful, MP will file for market authorization of the M6229 drug product. MP will adhere to the code of "Maatschappelijk relevant licentiëren".
7 The project is a collaboration between different medical disciplines of Maastricht University Medical Centre, Department of Biochemistry of Maastricht University and the Biotech Company Matisse Pharmaceuticals.
8 The project aims to deliver a therapy that improves survival, reduces hospital stay, prevents the long term sequelae and morbidity of COVID-19.
9 The project aims to deliver a therapeutic concept that lessens the burden on society during the gap between the beginning of a pandemic by a new variant of coronavirus and the availability of an effective vaccine. This project could add a separate domain to the REMAP-CAP platform.

5. DEELNAME VAN DE STAKEHOLDER(S) (e.g. patiënten, zorgprofessionals, etc.):

Clinicians treating COVID-19 patients
Basic Scientists
Patients
Life Science Industry

6. LITERATUURREFERENTIES (optioneel):

1. Barnes, B. J. *et al.* Targeting potential drivers of COVID-19: Neutrophil extracellular traps. *J. Exp. Med.* **217,** 135–7 (2020).
2. de Bont, C. M., Boelens, W. C. & Pruijn, G. J. M. NETosis, complement, and coagulation: a triangular relationship. *Cell* 5126 *Immunol* **16,** 19–27 (2018).
3. Xu, J. *et al.* Extracellular histones are major mediators of death in sepsis. *Nature Medicine* **15,** 1318–1321 (2009).
4. Wildhagen, K. C. A. A. *et al.* Nonanticoagulant heparin prevents histone-mediated cytotoxicity in vitro and improves survival in sepsis. *Blood* **123,** 1098–1101 (2014).