Algemene gegevens / General Information

Programma / Programme	:	**COVID-19 Programma**
Subsidieronde / Subsidy round	:	**Bottom-up ronde COVID-19 aandachtsgebied 1**
Projecttitel / Project title	:	**A clinical trial targeting the kallikrein-kinin system in COVID-19 to prevent ARDS**
Projecttaal / Project language	:	**Engels / English**
Geplande startdatum / Planned start date	:	**01-06-2020**
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
- Virus, immuniteit, immuunrespons en pathogenese

1.2 Subthema aandachtsgebied 1
- RCT studie via REMAP-CAP

1.3 Setting
- Ziekenhuiszorg

Samenvatting / Summary

Within the current COVID-19 Public Health Emergency of International Concern, understanding the effectiveness of treatment strategies in patients with proven infection that focus on reduction of virus-induced clinical complications is urgently needed. Patients with COVID-19 can present with pulmonary edema early in disease. We have proposed that this is due to a local vascular problem because of activation of bradykinin 1 receptor (B1R) and B2R on endothelial cells in the lungs, with this angioedema being kinin-dependent. We have already conducted a proof of concept study with B2R antagonist icatibant, providing evidence for the involvement of the kallikrein-kinin system. However, icatibant has some shortcomings.
Now, we hypothesize that targeting the kallikrein-kinin system by inhibiting plasma kallikrein with lanadelumab has the potential to prevent acute respiratory distress syndrome in patients hospitalized with symptomatic COVID-19. We will conduct a proof of concept study to investigate whether intravenous lanadelumab can lower oxygen need and prevents resurgence of oxygen need during COVID-19 infection and is safe in COVID-19 patients. Moreover, we will study the effects of plasma kallikrein inhibition on immunological and kinin specific signatures and perform PK/PD of intravenous lanademulab in COVID-19 patients. Finally, we will provide a rationale and data on lanadelumab to implement this strategy in REMAP-CAP globally.
This study must be considered as an experimental domain for REMAP-CAP. If we deliver the proof of concept of lanadelumab, the applicants of this proposal can introduce the strategy in REMAP-CAP globally.

Trefwoorden / Keywords

COVID-19; oxygen need; pulmonary edema; angioedema; vascular; kinins; kallikrein; lanadelumab; proof of concept; PK/PD; REMAP-CAP

Samenwerking / Collaboration

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

Ja / Yes

Inhoud / Content

Disciplines / Disciplines
- Infecties, parasitologie, virologie / Infections, parasitology, virology

Financiële gegevens / Financial data

ZonMw budget

	Jaar / Year								
Kostenpost	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	**Totaal / Total**
Personeel	(10)(1c)								
Materieel									
Implementatie									
Apparatuur									
Overig									
Totaal / Total									

Co-financiering / Cofinancing

Naam co-financier / Name of cofinancier	Bedrag / Amount	Status
Takeda Nederland bv	(10)(1c)	Toegekend

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:

(10)(2e)

ORGANISATIE:

Radboud university medical center (Radboudumc), Nijmegen, The Netherlands

PROJECTTITEL:

A clinical trial targeting the kallikrein-kinin system in COVID-19 to prevent ARDS

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: Klik of tik om tekst in te voeren.
Instituut: Radboud Institute for Molecular Life Sciences (RIMLS)
E-mail: Klik of tik om tekst in te voeren.
Was aanwezig bij de webinar: ☐ Ja ☐ Nee

☒ Ik heb nog geen datasteward.
We zullen zsm een datasteward in het project betrekken. Financiën zijn hierop vooruitlopend al gereserveerd.

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

1. PROBLEEMSTELLING EN DOELSTELLING(EN):

Background.

On January 30th 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern. An important component of this urgently needed knowledge includes understanding the effectiveness of treatment strategies in patients with proven infection that focus on reduction of virus-induced clinical complications.

Patients with COVID-19 can present with pulmonary edema early in disease. We have proposed that this is due to a local vascular problem because of activation of bradykinin 1 receptor (B1R) and B2R on endothelial cells in the lungs (van de Veerdonk et al. eLife 2020). SARS-CoV-2 enters the cell via ACE2 that next to its role in RAAS is needed to inactivate des-Arg$_9$ bradykinin, the potent ligand of B1R. Without ACE2 acting as a guardian to inactivate the ligands of B1R, the lung environment is prone for local vascular leakage leading to angioedema. This will result in a sustained kinin-dependent local lung angioedema via B1R and eventually B2R activation. Kinins are produced by kallikreins, which are enzymes that process kininogens from plasma into kinins. These vasoactive kinins can in turn be inactivated by enzymes including ACE, ACE2, DPP4 and APP. Recently, we demonstrated the involvement of the kallikrein-kinin system (KKS) in a proof of concept study with B2R antagonist icatibant (Figure 1), which is further supported by:

1. A systems biology approach with targeted proteomics shows that COVID-19 have decreased SerpinA5 (which is an inhibitor of plasma kallikrein) and DPP4 (which degrades kinins) (van de Veerdonk et al., submitted)
2. A GWAS with 1000 COVID-19 patients from UK biobank reports one significant hit, which is in the gene encoding (Aminopeptidase P) APP, which is needed to degrade bradykinin https://news.bugbank.uk/2020/05/xpnpep2-is-genome-wide-significant-in.html.
3. Active plasma kallikrein is increased in patients with COVID-19. Treatment with icatibant, which blocks bradykinin signalling, resulted in a rapid and dramatic improvement in oxygen need in patients with COVID-19 (van de Veerdonk et al., submitted).

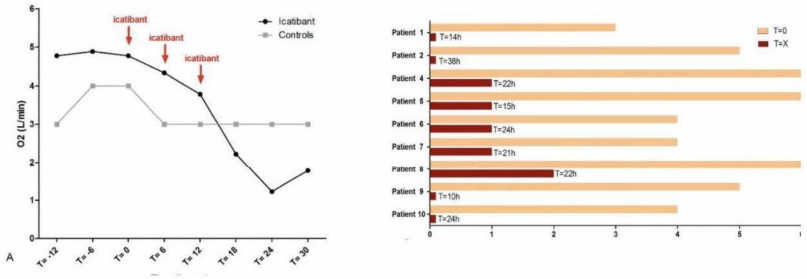

Figure 1. Oxygen supplementation in COVID-19 patients treated with icatibant versus controls. A. Median oxygen supplementation in patients with icatibant treatment (n=9) versus COVID-19 patients without icatibant treatment (n=27). B. Individual response of icatibant on oxygen (x-axis) and time of effect (T=X).

Although we confirmed our hypothesis with icatibant, this drug has shortcomings in the treatment of complications of COVID-19 disease. We observed a resurgence in oxygen need as the effect of icatibant weaned off within 36 hours due to the short half-life of icatibant of less than 2 hours. An upstream blockade of plasma kallikrein which is long lasting (half-life of approximately 15 days) is anticipated to overcome this

problem and most likely is more effective since it will not only block B2R effects but also B1R due to the reduction of their ligands.

Based on our proof of concept studies and knowledge ***we hypothesize that targeting the kallikrein-kinin system by inhibiting plasma kallikrein with lanadelumab has the potential to prevent acute respiratory distress syndrome (ARDS) in patients hospitalized with symptomatic COVID-19.***

Aims of the study:

1. Perform an experimental study to investigate whether lanadelumab can prevent ARDS by lowering oxygen need for a prolonged period of time in COVID-19 infection and is safe in this population.
2. To quantify the effects of plasma kallikrein inhibition on immunological and kinin specific signatures and perform PK/PD of intravenous lanademulab in COVID-19 patients.

This study must be considered as an experimental domain for REMAP-CAP. If we deliver the proof of concept in an intervention study with lanadelumab, the applicants of this proposal can introduce the strategy in REMAP-CAP globally as they are the appointed leaders of this specific ACE2-KKS domain in the REMAP consortium.

2. PLAN VAN AANPAK:

AIM 1. Perform an experimental study to investigate whether lanadelumab can prevent ARDS by lowering oxygen need for a prolonged period of time in COVID-19 infection and is safe in this population.
Study design: prospective, open label study performed in 10 centres in the Netherlands.
Study population: The proposed study is an open-label, intervention study in patients tested positive for SARS-CoV-2. Twenty patients that are on the general ward that are considered severe cases (SWAB case definition) will be enrolled. Inclusion criteria are the following: Patients will be 18 years and older, Oxygen saturation of <90% without supplemental oxygen and/or need of ≥ 3L/min supplemental oxygen. Exclusion criteria are: Acute myocardial or cerebral ischemic event at time of enrolment; Receiving an agent that is specified as an intervention in this domain; A baseline alanine aminotransferase or an aspartate aminotransferase that is more than five times the upper limit of normal; known hypersensitive to full human monoclonal antibodies. Lanadelumab will be supplied by Takeda (value 300,000 euro).
Intervention and comparator: lanadelumab 300 mg as intravenous administration on day 1 and day 4. For each patient treated with lanadelumab, three matched controls will be identified using the local registry of COVID-19 patients.
Outcome measures: Primary outcome measure will be the oxygen flow (in Liters/min) throughout a 14 day follow up (or until clinical discharge). Secondary outcome measures include ICU admission, general well-being, number of days in the hospital, and readmission within 14 days after start of lanadelumab.
Sample Size: As this is a proof of concept study we have chosen an empirical size of 20 patients.
Data-analysis: basic descriptive statistics. Health Evidence will assist in more in depth analysis and the analysis plan will be drafted prior to analysis.

AIM2. To quantify the effects of plasma kallikrein inhibition on immunological and kinin specific signatures and perform PK/PD of intravenous lanademulab in COVID-19 patients.
The pharmacokinetics of lanadelumab are unknown in patients after **intravenous** administration. All patients will undergo a repeated sampling on any day of lanadelumab treatment to quantify pharmacokinetics (n=12 sampling points). State of the art modeling and simulation techniques will be deployed using non-linear mixed effect modeling. Radboudumc will match the data from these patients with pre-existing data from Takeda (data transfer already completed). The final model will be used to simulate the pharmacokinetic behaviour. Besides clinical endpoints, we will investigate the effects of lanadelumab on the immune system and kinin system:
The following information will be assessed:

- Olink panels (inflammation and cardiometabolic) in EDTA plasma of COVID-19 patients.
- The capacity of PBMCs to produce proinflammatory cytokines (IL-1, TNF, IL-6) and adaptive cytokines (IFNγ and IL-17) in response to IL-1α, LPS, imiquimod (TLR7/8), *Staphylococcus aureus*, and *Aspergillus*.
- Kallikrein and functional KKS assays (Dr. Coen Maas) and mass spectometry of kinins in the circulation (collaborations: Dr. Marko Poglitsch (Vienna), and Prof. Stephanie Laeer (Dusseldorf))

These data will provide novel insight in disease mechanism of COVID-19 with emphasis on KKS, and will show the effects of targeting KKS on specific immune responses, kinin biology, and relevant proteins from Olink panels already identified playing a role in COVID-19 (van de Veerdonk et al., submitted).

This study must be considered as an experimental domain for REMAP-CAP. After we deliver the proof of concept the applicants will lead the global ACE2-KKS domain in the REMAP consortium and implement findings into this large trial. For this we have the following additional strategy:

IMPLEMENTATION. To implement lessons learned from our strategy in REMAP-CAP globally.
The use of vaccination, antivirals, and host-directed therapy in COVID-19 cannot be seen separate and needs specific timing for each of these strategies. Therefore, we do not see targeting the KKS as a treatment on its own but as a strategy that needs to be integrated in a treatment strategy for COVID-19.

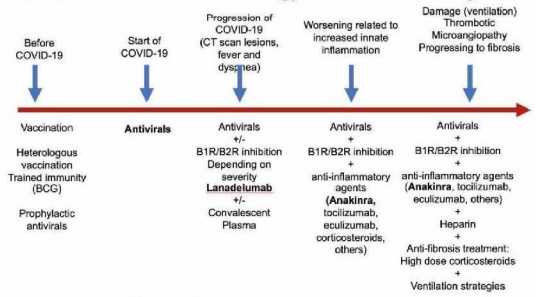

Figure 2. Schematic representation of treatment strategies for COVID-19 and their timing. We envisage that the triple strategy of an effective antiviral, lanadelumab, and anakinra has the potential to prevent patients from ICU admission and mortality. This strategy will allow us to vaccinate and get herd-immunity without burden on health care and with less mortality than influenza.

Lanadelumab is licensed as subcutaneous injection to prevent hereditary angioedema. In our protocol both targeted disease (COVID) as well as the route of administration of lanadelumab are not approved in the US and Europe. Data generated will allow for an IMP to be drafted and knowledge translated to a large trial in REMAP-CAP. An Investigational New Drug request is submitted to FDA. One deliverable of this proposal will be a written protocol to implement in REMAP-CAP. Principal investigators of this protocol are in the lead of the ACE2/KKS domain in REMAP-CAP. We have strategically positioned the Netherlands as leading country. Lanadelumab will be trailed in moderate and severe COVID-19 patients and will be designed in such a way that we can test our idea of a triple strategy to prevent progression of disease (Figure 2 in bold: antivirals, KKS targeting, and an antiinflammatory. This has the capacity to stop progression of COVID-19 before the need of anticoagulation, antifibrotic therapy, and ICU admission. An important note is that once we have the deliverable of the clinical trial we can decide to implement in REMAP-CAP, this is expected within 3-4 months after start of the trial.

3. HAALBAARHEID VAN HET PROJECT:

Ethical approval is already obtained for PK/PD study. The clinical study protocol of intravenous lanadelumab is submitted. Patient recruitment will start as soon as the protocol is reviewed and approved (expected to be June 15). Follow-up: 6 months for clinical study, 3 months for PK analysis, 4 months for PKPD analysis, 3 months for drafting the report, 3 months for implementation and discussion.
MOTIVATION FEASIBILITY. The project group and participants have collaborated previously on a wide variety of infectious disease topics. Data collection using a protected web-based database (CASTOR) proved feasible for the sites to submit patient and microbiological data for the studies and will be used again for the proposed study. We have involved key players in the application: (i) the REMAP consortium, which can facilitate the recruitment of patients, coordinate biobanking, collection of data and epidemiological expertise, and is also instrumental in translating the outcomes of the study into public health measures and National treatment guidelines (SWAB); and (ii) the necessary expertise in pharmacology as well as immunology. The implementation into REMAP-CAP is feasible since the applicant is part of the international steering committee (ITSC) of REMAP-CAP https://www.remapcap.org/remapcap-itsc and there is large support for exploring targeting KKS when there is a good rationale and data on lanadelumab iv. for which this proposal is key.

4. RELEVANTIE VOOR DE PRAKTIJK:

This proposal will focus on the area "Aandachtsgebied 1: thema's: behandeling en pathogenese" of the ZonMW call for COVID-19. Our proposal has the capacity to identify a relevant treatment strategy in COVID-19 and by repurposing the drug lanadelumab for COVID-19 can be rapidly implemented in a large randomized adaptive trial via REMAP-CAP. If proven effective, this would have enormous impact:

- Reduction of COVID-19 associated morbidity and mortality in COVID-19
- Reduction of health utilization (especially on ICU beds and length of stay in hospital)
- It would reduce the need for 'lock down' or other restrictive measures

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

Participation of patients is safeguarded through REMAP_CAP infrastructure. Additional stakeholders are the WHO (van de Veerdonk is a member of the WHO committee of ACE2 domain), the Stichting Werkgroep Antibioticabeleid, pharmaceutical company Takeda, competent authorities such as EMA, FDA and CBG.

Locatie: Amsterdam, NL

Datum: 14 Mei 2020

Betreft: Samenwerking

Beste Zon-MW office,

Middels dit schrijven willen wij te kennen geven een recente samenwerking te hebben gestart met de onderzoeksgroep van Prof. Dr. Frank van de Veerdonk, Radboud Universiteit, Nijmegen.

Toen bleek dat Prof. Van de Veerdonk een COVID-19 gerelateerde aanvraag heeft ingediend bij Zon-MW. Wij zouden daar graag aan toevoegen dat ons voorstel geheel complementair is aan zijn voorstel. Deze voorstellen zouden het best tot hun uiting komen als deze zij aan zij uitgewerkt zouden kunnen worden.

Aangezien de projecten elkaar aanvullen en daarmee versterken, verwachten wij dat het uitvoeren van beide projecten leidt tot een substantieel grotere klinische impact.

Wij geven u deze informatie graag mee in uw beoordeling van ons project.

Met vriendelijke groet,

Prof. Dr. Jaap D. van Buul	Dr. (10)(2e)	Prof. Dr. Frank van de Veerdonk
Projectleider	Groepsleider	Internist
(10)(2e)	(10)(2e)	(10)(2e)

Adres Prof. Dr. Jaap van Buul:

J.D. van Buul, PhD, Principal Investigator

Professor of Vascular Cell Biology
Molecular Cell Biology Lab at Dept. Molecular Cellular Haemostasis | Sanquin Research and Landsteiner Laboratory
Leeuwenhoek Centre for Advanced Microscopy (LCAM), section Molecular Cytology at Swammerdam Institute for Life Sciences (SILS) at University of Amsterdam
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* Lab website: www.sanquin.org/research/group-leader-overview/molecular-cell-biology/index
* Chair Dutch Endothelial Biology Society; www.debsociety.nl
* President Dutch Society for Cell Biology; www.cell-biology.nl