DSMB Charter

(April 2020)

Full title	PRAETORIAN-COVID: A double-blind, placebo-controlled randomized clinical trial with valsartan for PRevention of Acute rEspiraTORy dIstress syndrome in hospitAlized patieNts with SARS-COV-2 Infection Disease
Short title	PRAETORIAN-COVID
Document version	2.0
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Principal investigator	Dr. R van Kimmenade
Coordinating investigator	-
Sponsor	Radboud University Medical Center
Funding agency	Novartis
Number of participants	651
Number of sites	To be determined

Table of contents

1 Introduction

1.1 Trial design

The current SARS-CoV-2 pandemic has a high burden of morbidity and mortality due to development of acute respiratory distress syndrome (ARDS). The renin-angiotensin-system (RAS) plays an important role in the development of ARDS, as known from the SARS and MERS epidemics as well as influenza and RS-virus pulmonary infections.

In patients with SARS, virus spike protein needs to bind to angiotensin-converting enzyme-2 (ACE2), which is necessary for the formation of an internalization complex. The subsequent downregulation of ACE2 has been shown to contribute to lung injury. The downregulation of ACE2 results in the excessive production of angiotensin II by the related enzyme ACE, and it has been suggested that the following stimulation of angiotensin II type 1a receptor (AT1R) increases pulmonary vascular permeability, thus potentially explaining the increased lung pathology when the expression of ACE2 is decreased. Indeed, it has been shown that in mice angiotensin receptor blockade (ARB) can protect against acute lung injury.

Thus, currently available ARBs , such as valsartan, may potentially block this pathological process mediated by angiotensin II. This may be accounted for by two complementary mechanisms: ARBs block the excessive angiotensin-mediated AT1R activation caused by the viral infection, and they upregulate ACE2, which reduces angiotensin II concentrations and increases the production of the protective vasodilator angiotensin 1–7.

The PRAETORIAN-COVID trial is a double-blind, randomized, placebo-controlled trial to investigate the effect of valsartan compared to placebo on the occurrence of ICU-admission, mechanical ventilation and death in adult hospitalized SARS-CoV-2-infected patients.

Adult hospitalized SARS-CoV-2-infected patients will be included within 24 hours after the diagnosis has been made. The active-treatment arm will receive valsartan in a dosage titrated to blood pressure up to a maximum of 160mg b.i.d. and the placebo arm will receive a matching placebo also titrated to blood pressure. Treatment duration will be 14 days or up to hospital discharge < 14 days or occurrence of the primary endpoint if < 14 days. Long-term mortality follow-up will be done until 1 year after randomization.

1.2 Outline of scope of charter

The purpose of this document is to describe the roles and responsibilities of the independent DSMB for the PRAETORIAN-COVID trial, including the timing of meetings, methods of providing information to and from the DSMB, frequency and format of meetings, statistical issues and relationships with other committees.

2 Roles and responsibilities

The aims of the committee are to safeguard the interests of trial participants, assess the safety and efficacy of the treatment during the trial, and to monitor the overall conduct of the PRAETORIAN-COVID trial.

The DSMB should receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the Principal Investigator (PI).

The DSMB's responsibilities are to:

- Conduct interim evaluation of the study, including aggregate and individual participant data related to safety, data integrity and overall conduct of the study;
- Make recommendations to the investigator(s) concerning continuation, termination, or other modifications of the study based on the observed beneficial or adverse effects of the study;
- Operate according to the procedures described in this charter and all procedures of the DSMB.

The DSMB should inform the PI if, in their view, it becomes evident that no clear outcome would be obtained or if the DSMB concluded there are important safety concerns.

3 Before or early in the trial

All potential DSMB members should have sight of the protocol/outline before agreeing to join the committee. If a potential DSMB member has major reservations about the trial (e.g. the protocol or the logistics) they should report these to the sponsor and may decide not to accept the invitation to join. DSMB members should be independent and constructively critical of the ongoing trial, but also supportive of aims and methods of the trial. It is recommended that, if possible, the DSMB meets before the trial starts or early in the course of the trial to discuss the protocol, the trial, any analysis plan, future meetings, and to have the opportunity to clarify any aspects with the principal investigators. DSMB members could formally register their assent by confirming (1) that they agree to be on the DSMB and (2) that they agree with the contents of this Charter.

3.1 Potential issues specific to the treatment under study: valsartan

Valsartan (brand name Diovan) is a nonpeptide, orally active, and specific angiotensin II receptor blocker acting on the AT1 receptor subtype. There is extensive experience with valsartan in patients with cardiovascular disease. In that setting, the safety profile is well-known. Side effects are rare around 2%.

As of yet, there is a scarcity of data on the use of valsartan in SARS-CoV-2-infected patients. In very preliminary data we see a (non-significant) negative correlation between the use of ARBs and number of SARS-CoV-2 deaths in Italy (data on file, prof A.H. Zwinderman, University of Amsterdam).

This is the first clinical trial to investigate the efficacy of ARBs in hospitalized patients with SARS-CoV-2 infection.

3.1.1 Drug side effects

The potential risks to study participants include drug side effects. The most frequent side effects (around 2% of patients) are: (orthostatic) hypotension, (orthostatic) dizziness, decreased renal function, decreased liver function.

In order to decrease chances of these side effects we will exclude patients with blood pressure less than 105/65 mmHg, estimated glomerular filtration rate < 30 ml/min/1.73m^2, or AST and/or ALT >3 times the upper limit of normal from participation.

Concerning hypotension, we expect in the valsartan group a drop in systolic and diastolic blood pressure of 16 and 12 mmHg at a maximum dosage of valsartan, respectively. A blood pressure at enrolment of 105/65 mmHg should ensure a mean arterial pressure of 65mmHg, allowing adequate end-organ perfusion. Moreover, dosage of study treatment will down- or uptitrated based on blood pressure according to predefined criteria, while based on the proposed mechanism of action vasopressive support is not contra-indicated.

3.1.2 Potential interactions

Simultaneous administration of aliskiren is generally not advised. Patients taking aliskiren are therefore excluded from participation.

3.1.3 Acute overdose

Clinical effects of an acute overdose are dizziness, tachycardia, hypotension, shock, cough, gastro-intestinal problems, reduced liver and kidney function, myalgia, muscle cramps, hyperkalaemia. Angio-oedema has seldomly been described, but could be life-threatening. Acute therapy comprises intensive hemodynamic monitoring. After ingestion, active carbon can be considered. In hypotensive patients, iv fluids should be administered. If this does not lead to the desired effect, dopamine or norepinephrine can be considered.

3.2 Potential issues specific to this study: SARS-CoV-2-infected patients

Since SARS-CoV-2 is a relatively new virus, we have yet to discover most of the aetiology and physiology of the virus. Caution has been warranted with regard to ARBs and ACE-inhibitors (ACE-I) in SARS-CoV-2-infected patients, as these drugs are known to increase ACE2 concentration, in relation to the observation that ACE2 is the cell entry site for the SARS-CoV-2. However, as stated by the "ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers" there is a lack of any evidence supporting harmful effect of ACE-I and ARB in the context of the pandemic SARS-CoV-2 outbreak. A recent publication by Kuster in the European Heart Journal concisely describes the controversy in a well-balanced manner and puts forward that ARBs may well have a protective effect.

In addition, a number of arguments also support the notion that increased ACE2 is actually beneficial:

1) An important risk for more severe SARS-CoV-2-infection is male sex as males have a clearly increased risk of worse outcomes. The ACE2 gene resides on the X-chromosome and indeed, having two copies, expression of ACE2 is 30% higher in females than in males (source: expression data GTEX);

2) Since ARBs increase concentrations of ACE2, any detrimental effect of higher ACE2 would lead to increased numbers of more severe SARS-CoV-2-infections in regions where more ARBs are used. However, the opposite is the case. In very preliminary data we see a (non-significant) negative correlation between the use of ARBs and number of SARS-CoV-2 deaths in Italy (data on file, prof A.H. Zwinderman, University of Amsterdam).

3.2.1 Literature

- www.farmacotherapeutischkompas.nl
- www.vergiftigingen.info
- www.covid19-druginteractions.org
- Kuster GM. SARS-CoV2: should inhibitors of the renin–angiotensin systembe withdrawn in patients with COVID-19? European Heart Journal. 2020.
- Vaduganathan M, Vardeny O, Pharm D, Michel T, Mc MJ, Pfeffer M, et al. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. N Engl J Med. 2020.
- Patel AB, Verma A. COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers: What Is the Evidence? JAMA. 2020.
- Bavishi C, Maddox TM, Messerli FH. Coronavirus Disease 2019 (COVID-19) Infection and Renin Angiotensin System Blockers. JAMA Cardiol. 2020.

4 Composition

One DSMB member will serve as Chair. The DSMB Chair will have served as a member and/or Chair of a DSMB for several studies and be willing to make firm commitment to participate as Chair for the duration of the study. Furthermore, the DSMB consists of one member with clinical expertise on SARS-CoV-2 and one statistician with knowledge about statistical methods for clinical research and analysis of research data.

The members will be independent of the trial (e.g. should not be involved with the trial in any other way or have some competing interest that could impact on the trial). Any competing interests, both real and potential, should be declared. A short competing interest form should be completed and returned by the DSMB members to the trial coordinating centre (Annex 1).

Chair: Prof. dr. W.H. van Gilst: (Professor of Cardiovascular and Clinical Pharmacology, University Medical Centre Groningen)
Clinical expert: Prof. dr. A. Vonk Noordegraaf (prof of Pulmonary Medicine, Amsterdam University Medical Centre, location VUmc)
Statistician: Prof. dr. J.G.P. Tijssen (professor of Clinical Epidemiology & Biostatistics, Amsterdam University Medical Centre, location AMC)

5 Relationships

Other than receiving compensation for their time spent as DSMB members from the sponsor, DSMB members should have no other relationship with the sponsor or funding agent that could impair the members' ability to objectively review study data.

DSMB members should have no direct involvement with the study investigators or intervention. Each member will sign a Conflict of Interest Statement prior to beginning service as a DSMB member, which includes current affiliations, if any, with any steering committees or advisory councils associated with the study, pharmaceutical and biotechnology companies (e.g., stockholder, consultant), and any other relationship that could be perceived as a conflict of interest related to the study and/or associated with commercial or non-commercial interests pertinent to study objectives. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility (see Annex 1)

DSMB members should not use interim results to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products.

5.1 Confidentiality

All materials, discussions, and proceedings of the DSMB are privileged and confidential. DSMB members agree to use this information exclusively to accomplish the responsibilities of the DSMB. No communication of the deliberations or recommendations of the DSMB, either written or oral, may occur except as required for the DSMB to fulfil its responsibilities. Individual DSMB members are expected to maintain confidentiality regarding the study outside the DSMB (including, but not limited to the investigators, regulatory agencies, or sponsor) except as authorized by the DSMB.

6 Organization of DSMB meetings

It is recommended that, if possible, the DSMB meets before the trial starts or early in the course of the trial, to discuss the protocol, the trial, any analysis plan, future meetings, and to have the opportunity to clarify any aspects with the principal investigators. During this meeting the DSMB will discuss the number of DSMB meetings necessary.

This trial aims to include 651 patients. The DSMB will perform two different types of monitoring:

- Continuous monitoring: Every 48 hours the DSMB will monitor both treatment arms for safety. This analysis will include the occurrence of the primary endpoint and the occurrence of death and will be performed unblinded by the statistician.
- Interim analysis: The first interim analysis by the DSMB will be performed when data is available on 200 patients (≈ one third of total anticipated enrolment) and the second when data is available on 400 patients (≈ two thirds of total anticipated enrolment). The entire DSMB will discuss adverse events, protocol violations, enrolment summary and interim data coded by treatment arm.

The statistician of the committee will perform the continuous monitoring. If these analyses raise a safety concern, a meeting will be set-up between all members as soon as possible, preferably using a video conference call given the circumstances of the COVID-19 pandemic. In case the first safety analyses pose no concern, the intervals for continuous safety monitoring may be increased per discretion of the DSMB.

The interim analysis will be facilitated by the DSMB statistician, preferably using video conference call with all other members of the committee. A quorum, defined as the presence of the chair and the statistician, is required to hold a DSMB meeting. This meeting will consist of only closed sessions.

7 Trial documentation, confidentiality and communication procedures

Numbers of events and safety data acquired during the continuous monitoring will be reviewed primarily by the statistician of the committee. The statistician will write a short summary of these results after every analysis. This (and the actual data used for the analyses) will be stored separate from other trial documents so that no unblinded information will be shared with the unblinded study team.

DSMB members are not blinded to the treatment allocation. The DSMB will report its recommendations in writing to the sponsor's representative. However, if any important safety-concerns are raised during the trial, the DSMB will set up a meeting with the executive committee (including at least the leading trial coordinator) to discuss the recommendations of the DSMB regarding further trial conduct.
The DSMB members should store the papers safely after each meeting so they may check the next report against them. After the trial is reported, the DSMB members should destroy the interim reports.

8 Decision making

The DSMB does not make decisions about the trial, but rather makes recommendations to an appropriate executive committee or its Chair.

The DSMB will be responsible for the execution of the interim analysis and for making recommendations to the executive committee. The statistical guidelines are further specified in the interim analysis statistical plan in Annex 3 and 4.

Every effort should be made for the DSMB to reach a unanimous decision. If the DSMB cannot achieve this, a vote may be taken. Details of this vote should not be routinely included in the report to the sponsor as these may inappropriately convey information about the state of the trial data. It is important that the implications (e.g. ethical, statisticial, practical, financial) for the trial be considered before any recommendation is made.

Effort should be made for all members to attend. If, at short notice, any DSMB members cannot attend at all then the DSMB may still meet if at least the statistician and the Chair will be present. If the DSMB is considering recommending major action after such a meeting the DSMB Chair should talk with the absent member as soon after the meeting as possible to check that they agree. If they do not, a further teleconference should be arranged with the full DSMB.

If a member does not attend a meeting, it should be ensured that the member is available for the next meeting. If a member does not attend a second meeting, they should be asked if they wish to remain part of the DSMB. If a member does not attend a third meeting, they should be replaced.

9 Reporting

The DSMB will report their recommendations through a letter to the Sponsor's representative within 2 days. A copy of this letter will be kept in the trial master file. However, if any important safety-concerns are raised during the trial, the DSMB will set up a meeting with the executive committee (including at least the leading trial coordinator) to discuss the recommendations of the DSMB regarding further trial conduct.

Minutes will be made of the DSMB meetings regarding the interim analysis by one of the members. The DSMB chair should sign off any minutes or notes. The chair will write a short summary of these results after every analysis. This (and the actual data used for the analyses) will be stored separate from other trial documents so that no unblinded information will be shared with the unblinded study team. Minutes for closed sessions are stored together with the other confidential DSMB information (not accessible for the sponsor or other blinded members).

If the DSMB has serious problems or concerns with the sponsor's decision a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DSMB's concerns.

Depending on the reason for the disagreement confidential data will often have to be revealed to all those attending such a meeting. The meeting should be chaired by a senior member of the sponsor or an external expert who is not directly involved with the trial.

10 After the trial

At the end of the trial there will be no meeting to discuss the final data with principal investigators. Data will be interpreted by the investigator team. The principal investigator will ensure that the trial results will be published in a correct and timely manner. The DSMB may wish to be given the opportunity to read and comment on any publications before submission.

DSMB members should be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DSMB meetings should be included in the body of this paper.

Annex 1: competing interest form

Potential competing interests of Data Monitoring Committee members for the PRAETORIAN-COVID trial.

The avoidance of any perception that members of a DSMB may be biased in some fashion is important for the credibility of the decisions made by the DSMB and for the integrity of the trial.

Possible competing interest should be disclosed via the trials office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DSMB member should remove the conflict or stop participating in the DSMB. Table 1 lists potential competing interests.

Table 1: Potential competing interests

Stock ownership in any commercial companies involved
Stock transaction in any commercial company involved (if previously holding stock)
Consulting arrangements with the sponsor
Frequent speaking engagements on behalf of the intervention
Career tied up in a product or technique assessed by trial
Hands-on participation in the trial
Involvement in the running of the trial
Emotional involvement in the trial
Intellectual conflict eg strong prior belief in the trial's experimental arm
Involvement in regulatory issues relevant to the trial procedures
Investment (financial or intellectual) in competing products
Involvement in the publication

Please complete the following section and return to the trials office.

	No, I have no competing interests to declare
	Yes, I have competing interests to declare (please detail below)

Please provide details of any competing interests: _____

_____

_____

_____

_____

Name: _____

Signed: _____ Date: _____

Annex 2: report from DSMB to sponsor where no recommendations are being made

[Insert date]

To: Principal investigator

Dear dr. R van Kimmenade

The Data Monitoring Committee (DSMB) for the PRAETORIAN-COVID trial met on *[meeting date]* to review its progress and interim accumulating data. *[List members] attended* the meeting and reviewed the report.

We congratulate the trial organizers and collaborators on the progress and conduct of the trial and the presentation of the data. The trial question remains important and, on the basis of the data reviewed at this stage, we recommend continuation of the trial according to the current version of the protocol *[specify protocol version number and date]* with no changes.

We shall next review the progress and data *[provide approximate timing]*

Yours sincerely,

*[*Name of meeting Chair*]*
Chair of Data Monitoring Committee

On behalf of the DSMB (all members listed below)

DSMB members:
(1) [*Insert name and role*]
(2) [*Insert name and role*]
(3) [*Insert name and role*]

Annex 3: continuous monitoring

This monitoring will be performed every 48 hours by the statistician of the committee. In case the first safety analyses pose no concern, the intervals for continuous safety monitoring may be increased per discretion of the DSMB.
Possible recommendations after the interim analysis could include, but are not exclusive to:

- No action needed, trial continues as planned
- Early stopping due to harm of a treatment or clear superiority
- Sanctioning and/or proposing protocol changes

Overview of monitoring objectives

The objective of the continuous analysis will be to assess the safety of all study participants, including:

- Drug safety: Is there any difference in the safety profile between treatment groups? If yes, are these associated with drug administration?
- Mortality: is there any difference in mortality rates between included patients treated with valsartan and those treated with placebo? If yes, could this difference have important consequences for the safety of the trial participants?

Disposition of patients

- Screened patients are defined as any patient who originally met the inclusion criteria and signed the informed consent.
- Randomized patients consist of all screened patients with a treatment allocation recorded in the electronic case report form (eCRF), regardless of whether the treatment was given or not.

Analysis Populations

The intention-to-treat principle will be used for the analyses, i.e. in the analysis participants will be included in the randomized assignment study group.

Analyses

- Drug safety: DSMB will review the clinical safety data in an unblinded manner. At the discretion of the DSMB, all endpoints and (serious) adverse events can be made available to the committee. All appropriate safety measures will be summarized for the safety population by treatment for the treatment period. Safety measures will be reported per treatment group, the number (n) and percentage (%) of patients experiencing at least one event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.
- Mortality: only part of the primary endpoint will be the main parameter of interest for this safety analysis, defined as all-cause mortality.

Unblinding plan

The chair will be unblinded to patient-level data for the continuous analyses. Additional personnel may be unblinded as necessary. The DSMB will maintain a running log of personnel who have been unblinded, the date of unblinding, and the level of unblinding (group- or patient-level). Once unblinded, these personnel will have no further active role in the collection of outstanding clinical data or in making decisions on data handling. Unblinded personnel will have no further role in the programming of the analysis data sets and data displays after becoming unblinded. The sponsor will maintain a master list of all people who are unblinded.

Annex 4: interim analysis

Overview of monitoring objectives

The objective of the interim analysis will be to assess the following:

- Safety: is there any difference in the safety profile between treatment groups? If yes, are these associated with drug administration?
- Efficacy: is there a clear difference in outcomes between treatment groups?
- Are there any other observations in the accumulated data that should be communicated to the sponsor?

The primary composite endpoint (comprising of ICU admission, mechanical ventilation and mortality) will be the main parameter of interest for both safety as well as efficacy analyses.

This trial aims to include 651 patients. The first interim analysis by the DSMB will be performed when data is available on 200 patients and the second when data is available on 400 patients. Possible recommendations after the interim analysis could include, but are not exclusive to:

- No action needed, trial continues as planned
- Early stopping due to harm of a treatment or clear superiority
- Sanctioning and/or proposing protocol changes, such as a change in sample size in case of large discrepancies between expected and observed event rates in the control arm.

Disposition of patients

- Screened patients are defined as any patient who originally met the inclusion criteria and signed the informed consent.
- Randomized patients consist of all screened patients with a treatment allocation recorded in the electronic case report form (eCRF), regardless of whether the treatment was given or not.

Analysis Populations

The intention-to-treat principle will be used for the analyses, i.e. in the analysis participants will be included in the randomized assignment study group.
A subset analysis may be conducted with the per-protocol principle, i.e. all enrolled subjects who received and completed the randomized treatment assignment, and who had no pre-specified inclusion or exclusion violation as defined in this protocol.

Safety analysis

DSMB will review the clinical safety data in an unblinded manner. At the discretion of the DSMB, all endpoints and (serious) adverse events can be made available to the committee. The primary composite endpoint (comprising of ICU admission, mechanical ventilation and mortality) will be the main parameter of interest for safety analyses.

All appropriate safety measures will be summarized for the safety population by treatment for the treatment period. Safety measures will be reported per treatment group, the number (n) and percentage (%) of patients experiencing at least one event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Efficacy analysis

For efficacy, the primary endpoint is the main parameter of interest. Proportions will be calculated as described under “safety analysis”. Difference in proportion of primary outcome between intervention and control group will be tested at a prespecified p-value 0.001 at each interim analysis (recommended boundaries by Peto-Haybittle).

Unblinding plan

To assure blinding and independence interim analyses are discussed by the DSMB during the closed session. Data analyses are conducted by the independent statistician according to the plan described in this document.

All members of the DSMB will be unblinded to patient-level data for the interim analysis. Additional personnel may be unblinded as necessary. The DSMB will maintain a running log of personnel who have been unblinded, the date of unblinding, and the level of unblinding (group- or patient-level). Once unblinded, these personnel will have no further active role in the collection of outstanding clinical data or in making decisions on data handling. The unblinded statistician and other unblinded personnel will have no further role in the programming of the analysis data sets and data displays after becoming unblinded. The sponsor will maintain a master list of all people who are unblinded.

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
3. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020.
4. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020.