Inhaled Aviptadil for the treatment of COVID-19 in patients at high risk for ARDS: Study protocol for a randomized, placebo controlled multicentre trial.

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Research Article

Keywords: Aviptadil, VIP, COVID-19, ARDS, SARS-CoV-2

Posted Date: April 21st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1507210/v1

Abstract

Background: Despite the fast establishment of new therapeutic agents in the management of COVID-19 and large-scale vaccination campaigns since the beginning of the SARS-CoV-2 pandemic in early 2020, severe disesase-courses still represent a threat, especially to patients with risk factors. This indicates the need for alternative strategies to prevent respiratory complications like acute respiratory distress system (ARDS) associated with COVID-19. Aviptadil, a synthetic form of Human Vasoactive Intestinal Peptide, might be beneficial for COVID-19 patients at high risk of developing ARDS because of its ability to influence the regulation of exaggerated pro-inflammatory proteins and orchestrating the lung homeostasis. Aviptadil has recently been shown to considerably improve the prognosis of ARDS in COVID-19 when applied intravenously. An inhaled application of Aviptadil has the advantages of achieving a higher concentration in the lung tissue, fast onset of activity, avoiding the hepatic first-pass metabolism, and the reduction of adverse effects. The overall objective of this project is to assess the efficacy and safety of inhaled Aviptadil in patients hospitalized for COVID-19 at high risk of developing ARDS.

Methods: This multicentre, placebo-controlled, double-blinded, randomized trial with 82 adult patients hospitalized for COVID-19 and at high risk for ARDS (adapted early acute lung injury score ≥ 2 points) is conducted in four public hospitals in Europe. Key exclusion criteria are mechanical ventilation and severe hemodynamic instability. Patients are randomly allocated to either inhale 67µg Aviptadil or normal saline (three times a day for 10 days), in addition to standard care, stratified by centre. The primary endpoint is time from hospitalization to clinical improvement, defined as either hospital discharge, or improvement of at least two levels on the nine-level scale for clinical status suggested by the World Health Organization (WHO)

Discussion: Treatment strategies for COVID-19 are still limited. In the context of upcoming new variants of SARS-CoV-2 and possible inefficacy of the available vaccines and antibody therapies, the investigation of alternative therapy options plays a crucial role in decreasing associated mortality and improving prognosis. Due to its unique immunomodulating properties also targeting the SARS-CoV-2 pathways, inhaled Aviptadil may have the potential to prevent ARDS in COVID-19.

Trial registration: ClinicalTrials.gov, NCT04536350. Registered 02 September 2020, https://clinicaltrials.gov/ct2/show/NCT04536350

Introduction

Background and rationale {6a}

The world has been experiencing an exceptional state, due to the SARS-CoV-2 pandemic. In the beginning of 2020, about 20% of individuals with the associated corona virus disease (COVID-19) suffered from a severe course, characterized by significant respiratory symptoms including the potentially lethal acute respiratory distress syndrome (ARDS) (1). Since then, numerous studies have been initiated in order to

evaluate therapeutic agents for the treatment of COVID-19. To date, a reduction of mortality has been shown in randomized controlled trials for anti-cytokine monoclonal antibodies (tocilizumab), januskinase-inhibitors (baricitinb), and dexamethasone (2-4). At the time of setting up this study, other approaches like convalescent plasma and antiviral antibodies were being investigated (3, 5).

Despite the fast establishment and adaptation of recommendations for the clinical management of COVID-19, as well as large-scale vaccination campaigns, severe disease-courses still represent a threat, especially to patients with risk factors such as old age, arterial hypertension or diabetes mellitus (6). This indicates the need for alternative strategies to prevent and ameliorate respiratory complications associated with COVID-19, in order to effectively prevent intensive care (ICU) admissions and reduce mortality. The results of the RECOVERY trial indicate that an excessive inflammatory reaction plays an important role in the pathophysiology of severe COVID-19 and the progression to ARDS (2). In fact, severe cases of COVID-19 are associated with elevated serum levels of pro-inflammatory mediators (1, 7, 8). SARS-CoV-2 specifically targets the surfactant-producing pulmonary Alveolar Type II (ATII) cells by binding to their Angiotensin Converting Enzyme 2 (ACE2-) receptors and entering the cell (9). Viral replication and infection of adjacent ATII cells then lead to a massive cytokine release and, consequently, to apoptosis and a critical decrease of surfactant production, which disrupts the alveolar gas exchange resulting in ARDS (9, 10).

Vasoactive Intestinal Peptide (VIP), discovered and first synthesized in the seventies, has been proposed as a modulator of lung inflammation and airway constriction (11-13). Protective effects of VIP on pulmonary tissue have been shown in numerous animal models of lung injury in rats, guinea pigs, dogs and sheep (14-16). VIP was also shown to upregulate surfactant production and protect ATII cells by blocking virus replication, apoptosis, and cytokine effects (17-20).

Aviptadil, a synthetic form of VIP, might prevent COVID-19 patients from developing ARDS due to its anti-inflammatory properties. It has been shown to reduce interferon producing T-cells, to dampen Th17-T-cells and to promote regulatory T-cells (21-23). These immune-dampening effects have been previously described to occur in the alveolar compartment of sarcoidosis patients after inhalation of Aviptadil, which demonstrates that its local application by inhalation is feasible and results in relevant immunological changes (23). There is further promising evidence from a case report of a patient with pneumonitis resulting from check-point-inhibitor therapy for melanoma, in which the administration of inhaled VIP was well tolerated and led to dampening of alveolar inflammation, radiological and clinical improvement (24).

To date, there is no clinical evidence for the efficacy of inhaled Aviptadil in COVID-19. However, it was recently observed in vitro that VIP can inhibit SARS-CoV-2 replication and reduce cellular proinflammatory cytokine production (20). Two phase II trials have been announced recently on the U.S. National Library of Medicine platform “ClinicalTrials.gov” (COVID-AIV (NCT04311697), AVICOVID-2 (NCT04360096)), which investigate Aviptadil in patients with COVID-19 in the United States. Preliminary results of the COVID-AIV trial, which has been recruiting patients with COVID-19 and respiratory failure, indicate a promising antiviral effect of the intravenous administration of Aviptadil (25). In contrast, this current trial

investigates the inhaled application of Aviptadil in an earlier stage of disease, in patients at increased risk for ARDS. Inhaled Aviptadil likely circumvents several side effects, like hypotension and tachycardia (23, 24).

Daily doses of up to 300 µg inhaled Aviptadil have been shown to be safe in phase II trials for the treatment of sarcoidosis and pulmonary hypertension, as well as in a recently published phase I trial in the treatment of ARDS (23, 26-28). Aviptadil has been given Orphan Drug Designation in the European Union and the U.S.A. for the treatment of ARDS and the inhaled application has been observed to be safe without severe side effects (23, 24, 29).

Objectives {7}

The primary objective of this trial is to investigate the efficacy and safety of inhaled Aviptadil in hospitalized COVID-19 patients at high risk for developing ARDS. The study will assess whether patients with COVID-19 under high risk for developing ARDS recover faster when they receive inhaled Aviptadil in addition to standard care, compared to patients receiving standard care only. A secondary objective is the investigation of the overall course of disease under inhaled Aviptadil in terms of need for mechanical ventilation, time requiring oxygen supplementation, infection-related biomarkers, and subjective severity of symptoms. The safety objective is to assess any potential harm of inhaled Aviptadil.

Trial design {8}

This study is a multicentre, placebo-controlled, double-blinded, randomized phase II trial with 82 adult patients. In a parallel group design, patients will be randomly allocated in a 1:1 ratio to inhale either Aviptadil (67µg three times a day) or normal saline (three times a day) for 10 days, or until hospital discharge, in addition to standard care. The study is conducted as a superiority trial.

Methods: Participants, Interventions And Outcomes

Study setting {9}

Recruitment of hospitalized patients takes place at the Cantonal Hospitals of Liestal and St. Gallen and the Hospital Schwyz in Switzerland, as well as the Clinic Hietzing, Vienna in Austria and the Antonius Hospital Nieuwegein in the Netherlands between May 2021 and December 2022 (estimated).

Eligibility criteria {10}

Hospitalized patients with diagnosed COVID-19 are asked to take part in this study when the following eligibility criteria are fulfilled:

- SARS-CoV-2 infection, verified according to current in-house guidelines
- High risk for the development of ARDS:

I.e. within 24 hours before inclusion at least 2 points on an adapted EALI (early acute lung injury) score ≥ 2 points, with at least one point from the original EALI score (30, 31)

- Original EALI Score:
  - 2-6l O_2 supplementation to achieve a SaO_2>90%: 1 point
  - > 6l O_2 supplementation to achieve a SaO_2>90%: 2 points
  - Respiratory rate ≥ 30/min: 1 point
  - Immunosuppression: 1 point
- Modification adapting for risk factors for ARDS in COVID-19 affected patients (32)
  - Arterial hypertension: 1 point
  - Diabetes: 1 point
  - Fever > 39°C: 1 point
- Age ≥ 18 years
- Ability to comply with the inhalation maneuver
- Ability to understand the clinical trial and sign the informed consent

The presence of any of the following exclusion criteria will lead to exclusion of the participant:

- Mechanical ventilation or intensive care treatment within current hospitalization
- Nasal high-flow cannula or continuous positive airway pressure (cPAP) ventilation at time of inclusion
- Inability to conduct inhalation therapy
- Hemodynamic instability with requirement of vasopressor therapy
- Severe comorbidities interfering with the safe participation according to the treating physician
- Previous participation in this trial, or current participation in another interventional study
- Pregnancy

Systemic immunosuppression for chronic underlying condition (corticosteroid treatment as part of “standard care” allowed).

Who will take informed consent? {26a}

After a patient is identified as a potential participant, a GCP-trained physician from the study team will inform the patient personally about the trial and ask for written consent by signature on the informed consent form. Each potential participant will be informed that participation in the trial is voluntary, that

he/she may withdraw from the study at any time with no need of justification, and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. Consent or assent from authorized surrogates is not intended, patients who are not able to understand the trial or sign the informed consent form of their own accord are excluded from participation.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Additional collection and use of participant data and biological specimens are not intended.

Interventions

Explanation for the choice of comparators {6b}

Due to the novelty of the investigated disease COVID-19, global guidelines or a clear definition of standard care are not available at the time of implementation of the study. Additionally, standard treatment strategies may change during the study period in accordance with new research findings. At each study centre, there are internal written guidelines for the clinical management of hospitalized COVID-19 patients, depending on the severity of the case. At the time of implementation of the study, elements of the standard care used in the participating study centres include oxygen therapy, systemic glucocorticoids, antiviral treatment with remdesivir, nutritive measures, and prevention and management of ARDS, bacterial superinfections, sepsis, as well as thromboembolic, neurologic, cardiac and renal complications. Since there is no clear definition of standard care to date, the only ethically justifiable comparator is the best available care, which is adapted throughout the trial according to the current state of research.

Intervention description {11a}
Patients in the intervention group inhale 1ml Aviptadil solution (67 µg/ml) three times a day (morning, noon, evening), while participants in the control group inhale 1ml of NaCL 0.9% three times a day. In both groups, the respective treatment is given in addition to standard care and lasts for 10 days, or until hospital discharge, whichever occurs first. The study drug is administered with the M-neb® dose+mesh nebulizer MN-300/8 in both study groups and each application will approximately last for 10 minutes.

Criteria for discontinuing or modifying allocated interventions {11b}

Dose or device modifications are not intended. If clinically indicated, treating doctors can stop the treatment with the study drug. Participants are given the possibility to withdraw from the study at any time. Treating physicians can independently decide about additional treatment options and concomitant

medication can be re-evaluated and changed at any time of this trial. A termination of the supplementation is reported to the coordinating study centre immediately.

Strategies to improve adherence to interventions {11c}

All participants are hospitalized and medication is administered by qualified ward personnel. Ward personnel is responsible that participating patients receive the study medication in a correct manner and each administration will be documented in the patient history. Any complication or non-adherence with the administration is reported as a note to file.

Relevant concomitant care permitted or prohibited during the trial {11d}

All treatments considered necessary by treating doctors are permitted and their use is recorded in the case report form. Because inhaled Aviptadil does not reach the systemic circulation and is mainly metabolized in the lung, pharmacokinetic interactions with Aviptadil are not expected. In order to account for potential bias, we aim to analyse data from patients separately, who received concomitant treatment during the study period, that may bias the study results significantly (e.g. immunosuppressants or immunomodulators).

Provisions for post-trial care {30}

Patients are carefully monitored until discharge from the hospital. Necessary after-care is organized by treating physicians independent of this trial. Any potential damage or harm to participants in connection with this trial is covered by the obligatory trial insurance.

Outcomes {12}

The primary endpoint is time to clinical improvement up to day 28, defined as the time (in days) from randomization to the decrease of at least two levels on the WHO-suggested nine-level ordinal scale (see Table 1, (33)) or alive discharge from hospital, whichever occurs first. This standardized primary endpoint allows comparison with other efficacy studies in the context of the treatment of COVID-19.

Table 1: WHO-Ordinal scale for clinical improvement

Patient State		Descriptor	Score
Uninfected		No clinical or virological evidence of infection	0
Ambulatory		No limitation of activities	1
		Limitation of activities	2
Hospitalized Disease	***Mild***	Hospitalized, no oxygen therapy	3
		Oxygen by mask or nasal prongs	4
Hospitalized Disease	***Severe***	Non-invasive ventilation or high-flow oxygen	5
		Intubation and mechanical ventilation	6
		Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead		Death	8

From: WHO R&D Blueprint, novel Coronavirus COVID-19 Therapeutic Trial Synopsis (33)

RRT: Renal replacement therapy, ECMO: Extracorporeal membrane oxygenation

Key secondary endpoints are:

- Need for mechanical ventilation and intensive care during hospitalization
- Occurrence of multi organ dysfunction syndrome during hospitalization
- Number of days requiring oxygen supplementation
- Change from baseline to discharge of the following biomarkers in patients' blood samples
    - C-reactive protein (CRP)
    - Neutrophil-lymphocyte ratio
    - Interleukin-6

    - Procalcitonin
- Patient-reported impact on health by 12-item Short Form Survey version 2 (SF-12v2) at follow-up

Other clinical endpoints include the length of hospital stay until discharge or death (in days) and mortality rate. CRP, Interleukin-6, and procalcitonin are measured at baseline, at least every seven days, and at discharge. The safety endpoints adverse events (AEs), including those leading to discontinuation of treatment, serious adverse events (SAEs), and death are also reported.

Participant timeline {13}

The participant timeline is exhibited in Figure 1.

Sample size {14}

We assume that patients in the experimental group will show a twofold hazard to have a clinical improvement as compared to patients in the control group, based on the effect of Aviptadil described above. Furthermore, we assume an overall probability of reaching the endpoint within 28 days of 70% (34, 35). A sample size of 82 provides the trial with 80% power to detect a hazard ratio of 2, at a two-sided significance level of $\alpha=0.05$, as calculated using the formula in Chow (36).

Recruitment {15}

All hospitalized patients at a study centre who fulfill the eligibility criteria are asked to take part in this study. In order to reach the target sample size within the planned time frame, the study is geographically expanded to several centres within Europe.

Assignment of interventions: allocation

Sequence generation {16a}

The group-allocating randomization code is a computer-generated sequence, using block randomization with block size of four. Each block determines assignment of four patients to the two groups, while two patients are assigned to the intervention group and two patients are assigned to the control group in a random order. Randomization is stratified by study centre in order to account for differences in standard of care. Block randomization also accounts for differences in standard of care according to time elapsed since the start of the pandemic.

Concealment mechanism {16b}

The entire concealment process is handled in the pharmacy that produces the study drug. Identically looking vials with doses of either 3 ml Aviptadil solution (67µg/ml, experimental group) or 3 ml NaCl 0.9% (placebo group) are filled in the pharmacy in a 1:1 ratio. Kits of 10 vials of the same content (one vial per treatment day, for a maximum of 10 days) are then packed and labelled with a continuous kit number. The actual content of each kit (Aviptadil or placebo) is determined by the randomization sequence described above, while the kit number represents the concealed randomization code. For each kit, the description of the actual content (Aviptadil or placebo) is packed in a separate concealed envelope, with only the kit number visible from the outside. The respectively allocated kits and concealed envelopes are shipped to the coordinating study centre in Liestal. From here, they are distributed to each study centre and used in the order of the kit number indicated on the label. Upon inclusion of a patient, the allocated kit number is documented in the CRF. The concealed envelopes containing the description of group allocation are stored at the coordinating study centre in Liestal.

Implementation {16c}

The entire concealment process is handled in the pharmacy that produces the study drug. Study physicians at the respective study center will enroll participants into the study and hand out the kits containing the study drug in the order of the assigned kit numbers. Group assignment is pre-defined by order of the kit numbers and the content of the respective kit.

Assignment of interventions: Blinding

Who will be blinded {17a}

Trial participants, investigators, treating physicians, study personnel administering the inhalation, and data analysts are blinded to group allocation. Since the study drug is filled into identically looking vials and Aviptadil solution and placebo are not visually distinguishable, blinding is ensured until unblinding procedures are actively undertaken.
Procedure for unblinding if needed {17b}

If a treating physician of a participating patient needs to know for medical reasons (i.e. AE, SAE), if the patient is assigned to the interventional or control group, he/she can call a 24h phone hotline to receive information about the patient's group allocation. Unblinding is undertaken by a trained study team member, who opens only the envelope with the respective kit number.

Data collection and management

Plans for assessment and collection of outcomes {18a}

All required patient data at baseline, during hospitalization, at discharge and follow-up are recorded on paper-based case report forms (CRFs). Trained study personnel at each site transfer the data into a web-based electronic case report form. A copy of the CRF used in the trial is available on reasonable request. Laboratory analyses comprise only standard parameters and are performed in the accredited in-hospital laboratories at each site. Patient dyspnea is assessed at inclusion and follow-up by means of the Medical Research Council dyspnea scale (MRC), which has been studied in a variety of respiratory conditions, including COVID-19. Patient-reported outcome is assessed at follow-up by means of the instrument SF-12v2, which is a validated survey for investigating health-related quality of life in a variety of both acute and chronic conditions, including lung diseases.

Plans to promote participant retention and complete follow-up {18b}

Patients participating in the study do not receive financial reimbursement. Expenses for the study medication and diagnostics performed only during this study are covered by the study budget. The 28-day follow-up is a phone call, initiated by a study team member at the respective study centre. In case of withdrawal of consent or premature termination of the study, data and samples are evaluated in encrypted form until termination of the study.

Data management {19}

Data acquisition and entry into the the web-based and password protected electronic data capture system (SecuTrial®) are performed by trained staff at the participating study centres. Personal contact information, which is needed for follow-up phone calls, is stored separately and only accessible for the staff members executing these phone calls. Any paper documents, such as Informed Consent Forms, are stored in locked cabinets in restricted access areas at the respective participating study centres. Electronic records are stored on a password-protected server. All records are archived for a minimum of ten years after study termination or premature termination of the clinical trial at the respective participating study centre. A data management plan documents details for the data processing and is available from the authors upon reasonable request.

Confidentiality {27}

All collected patient data are treated as confidential and stored and analyzed in a coded way in accordance with data protection principles. Results will be published in anonymized fashion. Direct access to source documents is permitted for purposes of monitoring, audits, and inspections. The study data and protocol shall be accessible to regulatory authorities for at least 10 years after study termination.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

The trial does not involve collecting biological specimens for genetic or molecular analysis.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

R will be used for all statistical analyses (37). Primary and secondary endpoints will be summarized using descriptive statistics (median and interquartile range for continuous outcomes, absolute frequencies and percentages for categorical outcomes). The primary endpoint “time to clinical improvement” will be portrayed by Kaplan-Meier plots and groups will be compared with a log-rank test. Hazard ratios with 95% confidence intervals will be calculated using the Cox proportional-hazards model in univariable and adjusted analyses (e.g. possible covariate is study centre). Where applicable, secondary endpoints will be analyzed by means of statistical testing: Group differences will be assessed using student t-test or, if not normally distributed, Mann-Whitney-U test for continuous outcomes and Pearson’s chi-squared test for frequencies. Detailed methodology for summaries and statistical analyses of the data collected in this trial is documented in a separate statistical analysis plan. The statistical analysis plan is finalized before database closure and can be obtained from the authors upon reasonable request.

Interim analyses {21b}

Since a relatively small number of patients is studied during a short study period (max. 28 days) and the treatment harm is considered to be very small due to the short treatment period, we do not consider stopping criteria nor interim analyses to assess the probability that the benefit exceeds the clinically important difference.

Methods for additional analyses (e.g. subgroup analyses) {20b}

See {20a}.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

The primary analysis will be done in the intention-to-treat population and safety analysis will be done on all patients who started their assigned treatment. The time to clinical improvement will be assessed after all patients will have reached day 28, with failure to reach clinical improvement or death before day 28 considered as right censored at day 28. Careful trial planning and conduct will minimize the occurrence of missing data as far as possible. In case of missing data, treating physicians are contacted with the aim to complete missing data from patients' records. No data imputation is planned.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

Further and updated trial information can be found at www.ClinicalTrials.gov, NCT04536350. Data and materials that support this protocol, such as a detailed data management plan, CRFs and informed consent form are available from the authors on reasonable request.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The coordinating study centre at Cantonal Hospital Baselland, Liestal, Switzerland, consisting of the Sponsor-Investigator, co-investigators, study coordinators, study physicians, study nurses, and study statistician supervises and coordinates the study. This includes trial management and coordination, statistical, economic and data management, as well as organizational support for participating study centres. It furthermore acts as a trial steering committee.

Composition of the data monitoring committee, its role and reporting structure {21a}

The monitoring of this study is performed by the independent Clinical Trial Unit (CTU) of the University Hospital Basel, Switzerland, in collaboration with qualified personnel of the coordinating study centre. Reporting is done directly to the Investigator. The CTU is independent of the sponsor and without competing interests.

Adverse event reporting and harms {22}

During the entire duration of the trial, all AEs and SAEs are collected, fully investigated, and documented, irrespective of whether they are related or unrelated. Participating study centres are obliged to report SAEs within 24 hours to the Sponsor-Investigator, who, in case of death, reports to the ethics committee within seven days. AEs and SAEs are followed up until resolution or stabilization. Adverse events will be reported in any associated relevant publication arising from this trial.

Frequency and plans for auditing trial conduct {23}

The study is conducted in accordance with the currently approved protocol, Good Clinical Practice (GCP) standards, and relevant regulations. Regular monitoring is performed following GCP and the trial monitoring plan. Data is evaluated for protocol compliance, integrity, and accuracy in relation to source documents. Authorities can audit this trial independently from the Sponsor-Investigator and the data monitoring committee. Study documentation and data are accessible to auditors and all involved parties must treat participant data as strictly confidential.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Important protocol modifications are submitted to the relevant authorities (ethics commission, local drug authorities) for approval before implementation. Changes are communicated to other relevant parties (investigators, study physicians, study nurses) via E-Mail newsletters and personal phone calls.

Dissemination plans {31a}

Our aim is to publish the results of this study in a peer-reviewed journal, without the engagement of professional writers.

Discussion

Our described study protocol presents the design for a randomized controlled trial to investigate the efficacy and safety of inhaled Aviptadil in patients hospitalized for COVID-19 at high risk for ARDS. In the context of upcoming new variants of SARS-CoV-2 and a possible future endemic state, the investigation of alternative therapy-options still plays a crucial role in decreasing associated mortality and improving prognosis. Due to its unique immunomodulating properties specifically targeting the SARS-CoV-2 pathways, inhaled Aviptadil may have the potential to prevent ARDS in COVID-19.

This trial is conducted in different European hospitals in order to ensure generalizability and meet the recruitment target. Patients of all adult age groups and with a wide range of co-morbidities are included

into the study, allowing for a broad representation of COVID-19 patients. The primary endpoint as suggested by the WHO allows a comparison with other investigated substances for the management of COVID-19. The evaluation of the secondary endpoints will give further insight into the effects of inhaled Aviptadil with regard to systemic inflammation markers, as well as patient reported outcomes.

Due to the novelty of the disease and new research results, standard care is constantly adapted, which may lead to changes in the relative effect of Aviptadil over time. However, the block-randomization with a small block-size of four ensures that this circumstance will not bias the results. Furthermore, with COVID-19 being the research focus of many current projects, which are “competing” for participating patients, recruitment may become difficult. This challenge is addressed by increasing the number of collaborating centres and assuring, that no competing projects are recruiting at the involved sites.

To date, there are no published data about the administration of inhaled Aviptadil in COVID-19. Because of the promising properties of Aviptadil, there is an urgent need to close this research gap with a well-designed randomized controlled trial. If the results of this study show that inhaled Aviptadil is effective and safe, they may ultimately lead to the introduction of a new substance for the management of COVID-19.

Trial status

The first patient was enrolled into this study on May 18th 2021. The study is currently ongoing with active recruitment under protocol Version 6, dated September 2nd, 2021. Recruitment is anticipated to be completed in December 2022.

Abbreviations

AE
adverse event
ARDS
acute respiratory distress syndrome
ATII
alveolar type-II
cPAP
continuous positive airway pressure
CRF
case report form
CRP
C-reactive protein
CTU
Clinical Trial Unit
DMC

data monitoring committee
EALI
early acute lung injury
EKNZ
Ethics Committee for the Region of Northwestern and Central Switzerland
EKOS
Ethics Commission for Eastern Switzerland
GCP
Good Clinical Practice
ICU
intensive care unit
SAE
serious adverse event
SF-12v2
12-item Short Form survey, version 2
VIP
vasoactive intestinal polypeptide
WHO
World Health Organization

Declarations

Acknowledgements

The authors thank Dorian Bevec, Alexander Brett, Helmi van Hirtum, Wolfgang Hoppe, Andrea Kloetzer, Sabrina Maier, Katrin Schmelzle, Philip Tarr, Sandra Widmer, the team from the CTU Basel, and all study physicians for guidance, assistance, support, protocol-conform implementation and valuable feedback.

Authors’ contributions {31b}

Sponsor-Investigator, responsibility for conception, design and supervision of the trial: JDL

Drafting of manuscript / Corresponding author: MBoe

Study concept and design: MBoe, KA, PH, JDL

Global study coordination: MBoe, KA

Administrative supervision and submission to relevant authorities: KA

Local study supervision / Principal Investigators: JDL, MBra, RN, JCG, WP

Statistical Analysis plan and sample size calculation: MBoe, SG

First version of protocol: JH, KA, ALT, JDL

Critical revision of manuscript for important intellectual content: MBoe, KA, MBra, MBru, EB, BCF, SG, JCG, PH, JH, FJ, ALT, GLC, JMQ, RN, WP, FR, JDL

All authors read and approved the final manuscript.

Funding {4}

This trial is mainly financed by AdVita Lifescience GmbH, Gundelfingen, Germany. In addition to financial and material support, AdVita Lifescience provides technical support for the used nebulizer devices. Qualified parties of the funding body share their prior experiences and knowledge about the investigational product with the study team in order to support with design-related and logistic decisions. However, the Sponsor-Investigator JDL takes full responsibility and ultimate authority for study design, data collection, data management, data analysis, interpretation of data, and decisions concerning publication. The Cantonal Hospital Baselland has full ownership of any study related patient data and results.

Furthermore, MBoe receives a personal research grant from the Swiss Academy of Medical Sciences within the program “Young Talents in Clinical Research”.

Availability of data and materials {29}

Data and materials that support this protocol, such as a detailed data management plan, CRFs and informed consent form are available from the authors on reasonable request. Following completion of the trial, anonymized datasets and statistical code used in this study will be available from the authors on reasonable request.

Ethics approval and consent to participate {24}

Ethics approval to conduct this trial has been first granted for the sites Baselland and St. Gallen by the Ethics Commission for North-Western and Central Switzerland (EKNZ) and the Ethics Commission for Eastern Switzerland (EKOS) on December 3rd 2020 (Project-ID: 2020-01902). Four amendments regarding additional study sites (Schwyz, Vienna, and Nieuwegein), eligibility criteria and structural changes of the CRF have been approved by the EKNZ and EKOS between December 2020 and September 2021. Furthermore, we are currently awaiting ethics approval from the local ethics committees for the study sites in Vienna (Austria) and Nieuwegein (Netherlands).

The trial meets the criteria and principles of the Declaration of Helsinki and has been registered in the Clinicaltrials.gov database (Trial registration number: NCT04536350).

Informed consent to participate in the trial is obtained by the recruiting study physicians from all patients prior to study entry. Each patient will be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time with no need for justification, and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. On the consent form, participants are asked for permission to use of their data should they choose to withdraw from the trial. Participants are also asked for permission for personal data being shared with regulatory authorities, when relevant. Furthermore, the patient will be informed on an obligatory basis that his/her medical records may be examined by authorized individuals other than their treating physician. All patients are covered by liability insurance for the total study duration.

Consent for publication {32}

No personal data of any patient is used in this manuscript, therefore a consent for publication is not needed.

Competing interests {28}

All authors declare that they have no competing interests with regard to this study.

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Figures

	Enrolment	Intervention			Follow-up		
	Day 0	*Day 1*	*... Day 7 ...*	*Day 10**	*(Days 14, 21,...)*	*Hospital Discharge*	*Day 28*
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Randomization	X						
INTERVENTION:							
Experimental arm: Aviptadil 67µg 3x/d		♦	—	♦			
Placebo arm: Placebo 3x/d		♦	—	♦			
ASSESSMENTS:							
Baseline parameters[1)]	X						
Laboratory samples[2)]	X		X		X	X	
Dyspnea, Cough, Fatigue[3)], MRC	X						X
Vital signs	X	♦	—	♦	—	♦	
Concomintant medication	X	♦	—	♦	—	♦	
Patient diary for COVID-19 symptoms	X	♦	—	♦	—	♦	
Summary of Hospitalization[4)]						X	
Self-reported survey of health - SF-12v2							X

Figure 1

Participant timeline.

*if hospital discharge occurs first, intervention is stopped at discharge.

[1)] Demographics, clinical status according to nine-level ordinal scale, medical history, smoking status, COVID-19 symptoms, COVID-19 vaccination status

[2)] C-reactive protein, neutrophil-lymphocyte ratio, interleukin-6, procalcitonin

[3)] On a visual analog scale from 0 to 10

[4)] Clinical status on nine-level ordinal scale, admission to ICU, ventilation, mortality, complications

MRC: Medical Research Council dyspnea scale

SF-12v2: 12-item Short Form Survey version 2