ACE inhibitors or ARBs discontinuation for Clinical Outcome Risk reduction in patients hospitalized for the Endemic Severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection: the randomized ACORES-2 study

Interventional research protocol involving human participants concerning a medicinal product for human use

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SIGNATURE page for a research PROTOCOL

Research code number: APHP200409

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The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

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1 SUMMARY

Full title	ACE inhibitors or ARBs discontinuation for Clinical Outcome Risk reduction in patients hospitalized for the Endemic Severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection: the randomized ACORES-2 study
Acronym/reference	ACORES-2/ APHP200409
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Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Since December 2019, a novel coronavirus called SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has caused an international outbreak of respiratory illness described as COVID-19. The full spectrum of COVID-19 severity is still being depicted (1,2). Individuals with a history of cardiovascular disease develop a more severe illness and have higher rates of death. In the landmark Chinese cohort study (n=1099), 23.7 % individuals with confirmed COVID-19 had hypertension, 16.2 % had diabetes and 8 % had a coronary or a cerebrovascular disease. As a result of these frequent comorbidities, individuals with COVID-19 are often treated with renin-angiotensin system (RAS) blockers, like angiotensin-converting enzyme (ACE) inhibitors and ARBs (angiotensin II receptor blockers). Because of the potential interaction between RAS blockers and SARS-CoV-2 mechanism of infection, there are ongoing scientific discussions on whether they should be stopped or continued in patients with COVID-19. SARS-CoV-2 infects human cells through the binding of its spike (S) protein to the membranous aminopeptidase

	called ACE2. Animal studies have demonstrated that RAS blockers increase the translation and synthesis of cardiac ACE2 and could therefore facilitate infection with SARS-CoV-2. The binding of the S protein to ACE2 leads to its downregulation in the infected cells, which has been shown to promote lung injury. Moreover, the continuation of RAS blockers could enhance acute kidney injury, which is frequent (6 to 10 %) in individuals developing severe COVID-19. On the other hand, the peptidase ACE2 has been shown to reduce inflammation and RAS blockers have demonstrated in animal studies a reduction in severe lung injury in certain viral pneumonias and therefore could be beneficial in COVID-19. ACE inhibitors may indirectly alter conformation of the ACE2 receptor binding domain binding site and affect its interaction with SARS-CoV-2. RAS blockers have also demonstrated benefits in individuals developing cardiac injury and myocarditis, which is a frequent complication of COVID-19. Eventually, the effect of RAS blockers discontinuation in clinically stable individuals with cardiovascular disease has been associated with an increase in major cardiac events. As a result, the discontinuation of RAS blockers in infected patients with cardiovascular disease could make them more vulnerable to a severe form of COVID-19. For all these reasons, it is crucial to determine whether RAS blockers should be discontinued or not in patients with COVID-19.
Main objective and primary endpoint	**Primary objective:** To compare the effect of discontinuation versus continuation of RAS blockers on the clinical course of patients with confirmed COVID-19 infection leading to hospitalization **Primary endpoint:** Time to clinical improvement from day 0 to day 28. Clinical improvement is defined as an improvement of two points on a seven-category ordinal scale, or live discharge from the hospital, whichever comes first, as recommended by the WHO R&D Blueprint expert group (3). The seven-category ordinal scale consisted of the following categories: 1. not hospitalized with resumption of normal activities

	2. not hospitalized, but unable to resume normal activities 3. hospitalized, not requiring supplemental oxygen 4. hospitalized, requiring supplemental oxygen 5. hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both 6. hospitalized, requiring ECMO, invasive mechanical ventilation, or both 7. death.
Secondary objectives and endpoints	**<u>Secondary objectives:</u>** 1. Evaluate the cardiovascular safety of RAS blockers discontinuation in patients hospitalized for COVID-19 by a composite endpoint of MACE. 2. Evaluate the efficacy of RAS blockers discontinuation in patients hospitalized for COVID-19 by the secondary efficacy endpoints. **<u>Secondary endpoints:</u>** **1. Primary safety endpoint:** major adverse cardiac events defined as the composite of cardiovascular death, myocardial infarction, stroke or acute heart failure at day 28. **2. Key secondary efficacy endpoints:** – Clinical status as assessed with the seven-category ordinal scale on day 28. – Number of days alive free of oxygen. – Number of days alive outside hospital during 28 days after randomization. – Number of days alive free of intensive-care unit (ICU) admission or mechanical ventilation (invasive or non-invasive) 28 days after randomization. – Number of days alive free of mechanical ventilation (invasive or non-invasive) 28 days after randomization. – Number of days alive free of ICU admission 28 days after randomization. – Rate of all-cause mortality at day 28. – Rate of cardiovascular death at day 28. – Number of days alive free of acute kidney injury during hospitalization.
Design of the study	**<u>Multicenter randomized controlled open label trial.</u>** This is a multicenter, randomized and controlled, open label trial in parallel groups among all patients on prior therapy with RAS blockers and diagnosed with COVID-19.

	Consecutive patients with a **diagnosis of COVID-19** confirmed by the presence of SARS-CoV-2 on any biological sample with any detection method requiring **hospitalization** will be enrolled. Patients will be **randomly assigned in a 1:1 ratio** to continue (group **continuation**) or not (group **discontinuation**) their usual RAS blockers therapy plus standard of care (oxygen, noninvasive or invasive ventilation, antibiotics, vasopressor support, renal-replacement therapy, circulatory assistance if needed). **The randomization will be stratified on the indication of RAS blockers** (heart failure vs. other indication). If the patients' usual treatment is not available in the hospital, a switch to ramipril for ACE inhibitors or valsartan for ARBs will be done in the continuation group or in case of cross-over. Written information consent will be obtained from all patients. All the medical data and outcomes will be record prospectively. **A phone call will be done at day 28** (± 4 days) for all survivor's patients.
Population of study participants	Adult patients with a diagnosis of COVID-19 requiring hospitalization and on prior therapy with RAS blockers.
Inclusion criteria	Subjects meeting all of the following criteria will be considered for enrolment into the study: 1. Age ≥ 18 year/old 2. Chronically treated with RAS blockers (ACE inhibitors or ARBs on the last prescription prior to admission with a treatment duration ≥ 1 month) 3. Diagnosis of COVID-19 confirmed by the presence of SARS-CoV-2 on any biological sample with any detection method 4. Patients hospitalized 5. Negative pregnancy test at inclusion visit for women of childbearing potential 6. Women of childbearing potential must agree to use adequate contraception according to Recommendations related to contraception and pregnancy testing in clinical trials, by Clinical Trial Facilitation Group (CTFG)
Exclusion criteria	Subjects presenting with any of the following will not be included in the study: 1. Shock requiring vasoactive agents

	2. Acute respiratory distress syndrome requiring invasive mechanical ventilation 3. Circulatory assistance 4. History of malignant hypertension according to the definition of the 2018 ESC/ESH guidelines on hypertension 5. Uncontrolled blood pressure despite the use of five antihypertensive drugs 6. History of nephrotic syndrome 7. History of hospitalization for hemorrhagic stroke in the past 3 months 8. RAS blockers therapy previously stopped > 48h 9. Pregnancy, breastfeeding 10. No affiliation to the French Health Care System "Sécurité Sociale" 11. Inability to obtain informed consent
Investigational medicinal product(s)	This is a study focusing on the evaluation of withdrawal of RAS blockers therapy (**discontinuation strategy**). No new treatment is being tested.
Comparator treatment	Pursuit of RAS blockers therapy (**continuation strategy**)
Interventions added for the study	**In the discontinuation strategy**: – For all patients randomized in the discontinuation group, an alternative treatment will be proposed according to the appropriate guidelines of the European Society of Cardiology (hypertension, heart failure, coronary artery disease) and the tolerance of the patient – In particular : – individuals at risk of uncontrolled blood pressure: consider calcium channel blocker as a first line option, if necessary other antihypertensive drug (non RAS blockers) can be added according to the physician decision – In individuals with history of heart failure: consider adding diuretics and nitrates (oral or IV according to the physician decision) – Reintroduction at the end of the study (day 28) according to the physician decision
Expected benefits for the participants and for society	Reduction of the risk of developing severe forms of COVID-19 by reducing the synthesis of ACE2 and the infection of patient's cells by the SARS-CoV-2. Reduce the delay to recovery and hospital discharge. Reduction of hypotension requiring vasopressors. Reduction of the rate of acute kidney injury. Better knowledge of the impact of RAS blockers on the acute lung injury related to coronaviruses.

	Better knowledge of the impact of RAS blockers withdrawal in cardiovascular high-risk patients.
Risks and burdens added by the study	Increase of cardiovascular events, such as acute heart failure, uncontrolled hypertension, myocardial infarction or stroke. Increase of COVID-19 related acute lung injuries by reducing the synthesis of ACE2 and angiotensin(1-7). Increase of COVID-19 related acute cardiac injuries, such as acute cardiac injury or myocarditis.
Practical implementation	The study will be proposed to all hospitalized patient which fulfill inclusion/exclusion criteria in participant sites. A reflection delay of 6 hours will be proposed to the patient. The consent form will be signed by both sides (patient and investigator) and the patient will be randomized. Hospitalized patients for a SARS-CoV-2 infection from all departments could be included (cardiology, infectious diseases, internal medicine…).
Number of participants included	554 (277 in each arm)
Number of centers	National study: 12 centers All departments with hospitalized patients for COVID-19 (cardiology, infectious diseases, internal medicine…)
Duration of the study	Inclusion period: 1 month Participation period: 28 days (± 4 days) Total duration: 2 months
Number of enrolments expected per site and per month	47 patients/site/month
Statistical analysis	This trial is designed in a public health emergency context, at which time there is limited information about clinical outcomes in Covid-19 hospitalized patients. We will include n=277 patients in each group to provide the trial with 90% power to detect a difference, at a two-sided global significance level of $\alpha = 0.05$, of 5 days in the median time to clinical improvement between the two groups, assuming that the median time in the standard-care group will be 16 days (B. Cao et al NEJM March 18th 2020). We considered 3 equally spaced analyses allowing early stopping for efficacy according to the O Brien-Fleming boundaries. Considering around 25 % of patients in the cardiac insufficiency stratum, we also checked that, in case of significant interaction between stratum and treatment due to a minor effect of the treatment in patients with cardiac insufficiency, this sample size will also allow 80%

	to detect a 5 days in the median time to clinical improvement in the other stratum that will include n=207 patients/group. Primary efficacy analysis will be on an intention-to-treat basis and included all the patients who had undergone randomization. The time to clinical improvement will be assess after day 28, and absence of clinical improvement or death before day 28 will be considered as right-censored at day 28. The time to clinical improvement will be analyze by Kaplan-Meier method and compare with a log-rank test.
Funding sources	In progress
Study will have a Data Safety Monitoring Board	Yes

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Hypothesis for the study

Since December 2019, a novel coronavirus called SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has caused an international outbreak of respiratory illness described as coronavirus disease 2019 (COVID-19). The full spectrum of COVID-19 severity is still being depicted (1,2).

Individuals infected with SARS-CoV-2 with a history of cardiovascular disease develop a more severe illness and have higher rates of death (2,4–8). In the landmark Chinese cohort study (n=1099), 23.7 % individuals with confirmed COVID-19 had hypertension, 16.2 % had diabetes and 8 % had a ischemic heart disease or a cerebrovascular disease (4). In the study by Yang et al., the most common comorbidities of 32 non-survivors from a group of 52 intensive care unit COVID-19 patients were diabetes (22%) and cardiovascular disease (22%)(9). In a study of 140 individuals admitted with COVID-19, nearly a third had a history of systemic hypertension (10).

In clinical practice, these frequent comorbidities are often treated with renin-angiotensin system (RAS) blockers, like angiotensin-converting enzyme (ACE) inhibitors and ARBs (angiotensin II receptor blockers); however, the baseline treatments of individuals infected with COVID-19 were not reported in either studies (2,4,7,9,11,11–13). In the PEACE population-based study on 1.7 million adults in China, it has been reported that 30.1 % of the Chinese adults between 35-75 years suffering from hypertension were receiving a treatment. RAS blockers were the second most commonly used medication (28.5 % of patients) (14).

ACE2 is a membranous aminopeptidase, homolog of ACE, which negatively regulates the renin angiotensin aldosterone system (RAAS) by converting Angiotensin II into Angiotensin-(1-7), a heptapeptide having a potent vasodilator function (15). It has been reported, from animal studies, that RAS blockers increase the translation and synthesis of cardiac ACE2 (16). As the SARS-CoV-2 infects human cells through the binding of its spike (S) protein to ACE2, it has thus been hypothesized that RAS blockers could, in fact, facilitate infection with SARS-CoV-2 (8).
Because of the potential interaction between RAS blockers and SARS-CoV-2 mechanism of infection, there are ongoing scientific discussions on whether they should be stopped or continued in patients with COVID-19. Several scientific societies have advised to not stop such treatments in patients with an underlying indication, albeit without experimental or clinical data (17).

For all these reasons, it is crucial to determine the effect of RAS blockers on outcomes of patients and infected by SARS-CoV-2.

We hypothesize that discontinuation of RAS blockers will reduce the time to clinical improvement in patients hospitalized for COVID-19 and treated with such agents prior to admission.

2.2 Description of knowledge relating to the condition in question

Coronaviruses are frequent human and animal pathogens (18). At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world. In February 2020, the World Health Organization formally designated the disease as COVID-19, which stands for coronavirus disease 2019 caused by SARS-CoV-2 (19).

By the end of March 2020, at least 300,000 confirmed cases have been reported in the world, including more than 80,000 in China and 16,000 in France. Increasing numbers of cases have been reported in other countries across all continents except Antarctica, and the rate of new cases outside of China has outpaced the rate in China.

Epidemiologic investigation in Wuhan identified an initial association with a seafood market that sold live animals. However, as the outbreak progressed, person-to-person spread became the main mode of transmission and is thought to occur mainly via respiratory droplets.

The incubation period for COVID-19 is thought to be within 14 days after exposure, with most cases occurring approximately four to five days after exposure (4,20).

In a report of 72,314 cases from the Chinese Center for Disease Control and Prevention, approximately 44,672 were classified as confirmed cases of COVID-19. A mild severity was reported in 81 % of patients, severe in 14%, critical in 5%, and the overall case fatality rate was 2.3 % (21). Eighty-seven percent of patients were between 30 and 79 years old.
In the published cohorts so far, most of the fatal cases have occurred in patients with advanced age or underlying medical comorbidities (including cardiovascular disease, diabetes mellitus, chronic lung disease, hypertension, and cancer) (2,4,5,7,21).

The most commonly reported symptoms at the onset of the illness were fever, fatigue, dry cough, anorexia, myalgia, dyspnea, sputum production (11).
The clinical suspicion is based on the association of fever, respiratory tract symptoms and a potential exposure within 14 days. The positive diagnosis is based on the detection of the SARS-CoV-2 by RT-PCR on a nasopharyngeal swab specimen, but the testing capacity is limited in France.

CT chest is also a useful exam as it may show specific radiological signs suggestive of viral pneumonias : bilateral ground glass opacity, consolidative abnormalities, fine reticular opacities, interlobular septal thickening and crazy paving (22–24). These abnormalities are more likely to be bilateral, have a peripheral distribution, and involve the lower lobes.
A study comparing CT-chest from patients with COVID-19 or with other viral pneumonia reported that radiologists were able to distinguish COVID-19 with high specificity but moderate sensitivity (25).
In fact, there has been some cases of negative RT-PCR despite CT-chest findings suggestive of a viral pneumonia in patients who were ultimately tested positive for SARS-CoV-2 (26).

In the published studies, the need for an admission in ICU varied from 5 to 32 %. The main causes for ICU admission were acute respiratory distress syndrome (ARDS, 3-42 %), shock (4-20 %), acute cardiac injury (7-17 %), acute kidney injury (3-15 %) (2,4,7,11–13).

Management of patients actually consists in a symptomatic treatment of organ failures. Several specific treatments are under evaluation, including antiviral (remdesivir, lopinavir-ritonavir), chloroquine and hydroxychloroquine, IL-6 inhibitor (tocilizumab), soluble human recombinant ACE2.

2.3 Summary of relevant pre-clinical experiments and clinical trials

There is an ongoing debate in the scientific community on whether RAS-blocker therapy should be discontinued in patients with COVID-19, owing to conflicting data and lack of evidence

A) There are possible deleterious effects of RAS blockers on COVID-19 patients:

- As previously described for SARS-CoV (15,27), SARS-CoV-2 infects human cells through the binding of its spike (S) protein to ACE2 receptors (28–31). It has been reported in animal studies that RAS blockers increase the translation and synthesis of cardiac ACE2 (16) and thus could facilitate SARS-CoV-2 binding to human cells (8). Nevertheless, absence of SARS-CoV was observed in some cells expressing ACE2, whereas infection was present in cells apparently lacking ACE2, suggesting that other factors are needed for cellular infection (32). It was also described an increase in urinary secretion of ACE2 in hypertensive patients treated with ARBs, suggesting an up-regulation of ACE2 by RAS-blockers in humans (33).

- The East Asian populations, particularly men, have a higher ACE2 expression in tissues which may suggest different susceptibility or response to SARS-CoV-2 from different populations under the similar conditions (34).

- The binding of the SARS-CoV-2 spike protein to ACE2 leads to ACE2 downregulation in the infected cells. This results in an overproduction of angiotensin by ACE and an increase in pulmonary vascular permeability by the stimulation of angiotension 1 (AT1) receptor, which has been shown to promote lung injury (35–37).

- On top of this potential physiopathogical link, the continuation of RAS blockers could enhance acute kidney injury, which is frequent (6 to 10 %) in individuals developing severe COVID-19.

B) On the other hand, there are also possible beneficial effects of RAS blockers on COVID-19 patients:

- The peptidase ACE2 has been shown to reduce inflammation (15) and RAS blockers have demonstrated in animal studies a reduction in severe lung injury with some viral pneumonias and therefore could be beneficial in COVID-19 (36–39). A treatment with

AT1R, could therefore protect against lung injury, by increasing ACE2 expression and angiotension-(1-7) production and reducing angiotensin II production (38–40).

- ACE inhibitors primarily target ACE which has 42% sequence identity with ACE2 and may be effective on ACE2 as well. They may indirectly alter conformation of the receptor binding domain (RBD) binding site and affect the interaction of ACE2 with SARS-CoV-2 (41).

- RAS blockers have also demonstrated benefits in individuals developing cardiac injury and myocarditis, which is a frequent complication of COVID-19 (6,7).

- Eventually, it is well described that the discontinuation of RAS blockers in clinically stable individuals with cardiovascular disease or hypertension is associated with an increased risk of major cardiac events, especially hospitalization for acute heart failure, recurrent myocardial infarctions or stroke (42–44). As a result, the discontinuation of RAS blockers in infected patients with cardiovascular disease could make them more vulnerable to a severe form of COVID-19.

2.4 Description of the population to be studied and justification for the choice of participants

The population of the study will be formed by adult patients with diagnosis of COVID-19 requiring hospitalization and on prior therapy with RAS blockers with a duration ≥ 1 month.

2.5 Identification and description of the investigational medication or medications

The ACORES-2 trial does not involve the use of an experimental medication (usual RAS blockers).
All the patients included in the ACORES-2 trial are already taking RAS blockers before participating in the research.
The experimental arm is therefore the discontinuation of this therapy.

2.6 Description and justification of the dosage, route of administration, administration schedule and treatment duration

The dosage will be the usual patient's one. In the continuation group, the treatment will be continued

RAS blockers are given according to the standard of care and the choice of the prescribed RAS blocker (INN and dosage) are unrelated to their participation in the research.

– For all patients randomized in the discontinuation group, an alternative treatment will be proposed according to the appropriate guidelines of the European Society of Cardiology (hypertension, heart failure, coronary artery disease) and the tolerance of the patient

In particular :

- in individuals at risk of uncontrolled blood pressure: consider Calcium Chanel blocker as a first line option, if necessary other antihypertensive drug (non-RAS blockers) can be added according to the physician decision
- In individuals with history of heart failure: consider adding diuretics and nitrates (oral or IV according to the physician decision)

2.7 Summary of the known and foreseeable benefits and risks for the research participants

The potentials benefits of discontinuation of RAS blockers for the participants are the following:

- Reduction of the risk of developing severe forms of COVID-19 by reducing the synthesis of ACE2 and the infection of patient's cells by the SARS-CoV-2
- Reduce the delay to recovery and hospital discharge
- Reduction of hypotension requiring vasopressors
- Reduction of the rate of acute kidney injury
- Better knowledge of the impact of RAS blockers on the acute lung injury related to coronaviruses.
- Better knowledge of the impact of RAS blockers withdrawal in cardiovascular high-risk patients

The potentials risk of discontinuation of RAS blockers for the participants are the following:

- Increase of cardiovascular events, such as acute heart failure, uncontrolled hypertension, myocardial infarction or stroke
- Increase of COVID-19 related acute lung injuries by reducing the synthesis of ACE2 and angiotensin(1-7)
- Increase of COVID-19 related acute cardiac injuries, such as acute cardiac injury or myocarditis

3 OBJECTIVES

3.1 Primary objective

To compare the effect of discontinuation versus continuation of RAS blockers on the clinical course of patients with confirmed COVID-19 infection leading to hospitalization

3.2 Secondary objectives

- To evaluate the safety of RAS blockers discontinuation on a composite endpoint of major adverse cardiac events defined as the composite of cardiovascular death, myocardial infarction, stroke or acute heart failure at day 28.

- To evaluate the efficacy of RAS blockers discontinuation:
  1. Clinical status as assessed with the seven-category ordinal scale on day 28.
  2. Number of days alive free of oxygen.

3. Number of days alive outside hospital during 28 days after randomization.
4. Number of days alive free of intensive-care unit (ICU) admission or mechanical ventilation (invasive or non-invasive) 28 days after randomization.
5. Number of days alive free of mechanical ventilation (invasive or non-invasive) 28 days after randomization.
6. Number of days alive free of ICU admission 28 days after randomization.
7. Rate of all-cause mortality at day 28.
8. Rate of cardiovascular death at day 28.
9. Number of days alive free of acute kidney injury during hospitalization.

4 STUDY DESIGN

4.1 Study endpoints

4.1.1 Primary endpoint

The primary endpoint of the study is the time to clinical improvement from day 0 to day 28, defined as an improvement of two points on a seven-category ordinal scale, or live discharge from the hospital (whichever comes first), as recommended by the WHO R&D Blueprint expert group (3).

The seven-category ordinal scale consisted of the following categories:
1. not hospitalized with resumption of normal activities
2. not hospitalized, but unable to resume normal activities
3. hospitalized, not requiring supplemental oxygen
4. hospitalized, requiring supplemental oxygen
5. hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both
6. hospitalized, requiring ECMO, invasive mechanical ventilation, or both
7. death.

4.1.2 Secondary endpoints

1. **Primary safety endpoint:** major adverse cardiac events defined as the composite of cardiovascular death, myocardial infarction, stroke or acute heart failure at day 28.

2. **Key secondary efficacy endpoints:**
   - Clinical status as assessed with the seven-category ordinal scale on days 28.
   - Number of days alive free of oxygen.
   - Number of days alive outside hospital during 28 days after randomization.
   - Number of days alive free of intensive-care unit (ICU) admission or mechanical ventilation (invasive or non-invasive) 28 days after randomization.
   - Number of days alive free of mechanical ventilation (invasive or non-invasive) 28 days after randomization.
   - Number of days alive free of ICU admission 28 days after randomization.

- Rate of all-cause mortality at day 28.
- Rate of cardiovascular death at day 28.
- Number of days alive free of acute kidney injury during hospitalization.

4.2 Description of research methodology

4.2.1 Design of the study

ACORES-2 will be a phase III national, multicenter, comparative, controlled, randomized, open label trial in parallel groups among patients hospitalized for COVID-19 and treated with RAS blockers.
It will test the superiority of the “discontinuation strategy” versus the “continuation strategy”.
Participants will be distributed in a 1:1 ratio between the 2 groups.

4.2.2 Number of participating sites

We are expecting to enroll 554 patients (277 in each arm) in 12 French centers.

4.2.3 Identification of participants

The participants in this research will be identified as follows:
Site number. (3 digits) - Sequential enrolment number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the study.

A randomization number will also be assigned when the participant is randomized. This number will have the following format: RXXX

4.2.4 Randomization

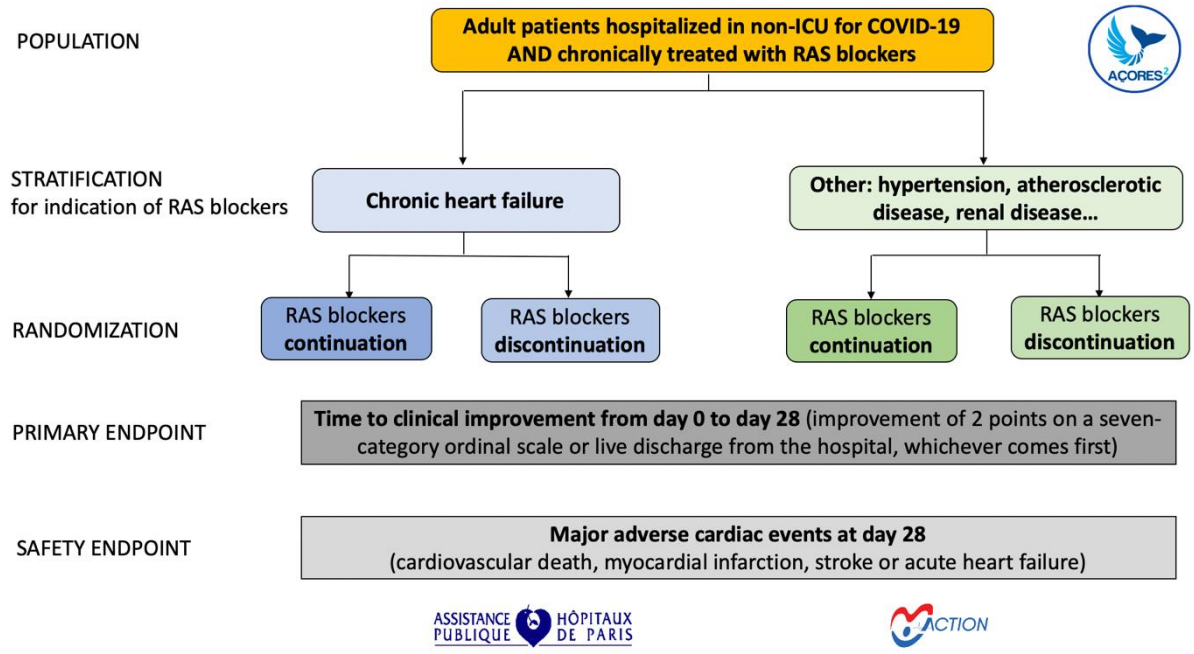
Randomization will be performed with IWRS (Cleanweb).
URC Lariboisière Saint-Louis will be done randomization list according to AP-HP Standard Operating Procedures (SOP).

Patients fulfilling the inclusion criteria and without any exclusion criteria that agree to enter the protocol and have signed the inform consent form during the consultation (inclusion) will be randomized in a 1:1 ratio to:

- Group Discontinuation = discontinuation of RAS blocker therapy until the end of the study which correspond to day 28 (experimental arm). After day 28, RAS blockers could be reintroduced or not, according to the physician decision.
  or
- Group Continuation = continuation of RAS blocker therapy (control arm)

The randomization will be stratified on the indication of RAS blockers (heart failure vs. other indication).

Inclusion and randomization will be done the same day.



5 IMPLEMENTATION OF THE STUDY

This study consists of the following study periods:

- Inclusion and randomization visit: inclusion and randomization during hospitalization
- Every day visit during hospitalization (until day 28, discharge or death): prospective collection of the events occurring during the index hospitalization until day 28, discharge or death
- Visit or phone call (for patients discharged from the hospital) at day 28 (± 4 days): collection of the events occurred since hospital discharge

5.1 Inclusion and randomization visit

This visit will take place within the framework of hospitalization for COVID-19.
In each 12 hospital of AP-HP, patients with a SARS-CoV-2 infection can be enrolled in any "non-ICU" department. In practice, considering the evolving situation in each hospital in Paris, patients could be included in any medical department: cardiology, infectious diseases, internal medicine, nephrology, endocrinology, neurology, pneumology. A coordinating investigator for each center will be designed to list all the co-investigators who can enroll patients.
After verification criteria for inclusion and non-inclusion, the investigator presents to the patient the ACORES-2 study and will be given time for reflection in order to obtain his participation agreement.
If the patient agrees to participate, the investigator will collect the written informed consent.

The patient will be included during the hospitalization in a study participating center.

Whose consent must be obtained	Who informs the individuals and collects their consent	At what point the individuals are informed	At what point the consent is obtained
The patient	Investigator (physician)	V0 visit (in-hospital admission)	After a reflection period of 6 hours at the latest after the patients' information

During this visit, the following data will be collected and some procedures and treatments will be carried out:

- Informed consent collection
- Inclusion/exclusion criteria review
- Demographic characteristics: date of birth, gender, height, and weight, blood group
- CV risk factors: smoking habits, diabetes, hypertension, dyslipidemia, family CAD, presence or not of a renal insufficiency (creatinine clearance ≤ 60ml/min)
- Medical and cardiovascular history: heart failure (with either preserved or reduced left ventricular ejection fraction), coronary artery disease, cerebrovascular disease, cardiomyopathy, valvular heart disease
- Other comorbidities: chronic lung disease, cancer, immunodeficiency, HIV
- Concomitant treatments at inclusion: mineralocorticoid receptor agonist, sacubitril, beta-blockers, calcium channel blockers, thiazides, loop diuretics, alpha-blockers, central acting agents, corticosteroids, nonsteroidal anti-inflammatory drugs
- Vital signs: pulse, blood pressure, respiratory rate, oxygen saturation, temperature
- Clinical status on a seven-category ordinary scale, as defined above
- Date of beginning of symptoms
- Symptoms compatible with SARS-CoV-2 infection: fever, cough, dyspnea, anosmia, ageusia, ocular congestion, myalgia, sputum production, anorexia, fatigue, headache, sore throat, rhinorrhea, digestive symptoms (diarrhea, nausea, vomiting)
- Complete physical examination
- Biology: complete blood count, creatinine, blood urea nitrogen, potassium, sodium, bicarbonate, alanine/aspartate aminotransferase, bilirubin, albumin, lactate dehydrogenase, prothrombin time, activated partial thromboplastin time, D-dimers, troponin I us, creatine kinase, natriuretic peptides (BNP or Nt-proBNP), C-reactive protein, procalcitonin, ferritin, arterial blood gas with lactate
- Blood group and rhesus will be determined at inclusion if not performed earlier. Data will be collected in the CRF. Indeed, it has been reported in 2,173 Chinese patients with COVID-19 that blood group A was associated with a higher risk for acquiring COVID-19 compared with non-A blood groups, whereas blood group O was associated with a lower risk for the infection compared with non-O blood groups. this observation was reported in a preprint article without peer-review and further investigation are of the relationship between the ABO blood group and the COVID-19

susceptibility is important (Zhao J, Yang Y, Huang H, Li D, Gu D, Lu X, et al. Relationship between the ABO Blood Group and the COVID-19 Susceptibility. medRxiv. 27 mars 2020;2020.03.11.20031096.)

Any arterial puncture for collecting arterial blood gas and/or lactate should be performed after topical anesthesia with lidocaine 5% cream (EMLA)"

5.2 Every day visit in hospitalization until day 28, discharge or death

The patients will have a daily visit during hospitalization until day 28, discharge or death.
All the events occurring during hospitalization will be collected prospectively, as well as the date of onset:

- Clinical status on a seven-category ordinary scale (as defined above) each day
- Hospital discharge
- Cross-over
- Cardiovascular death
- Non cardiovascular death and cause
- myocardial infarction
- Myocarditis
- Stroke
- Heart failure; presence of congestive signs, IV use of diuretics
- Acute kidney injury, as defined in the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines (45): increase in serum creatinine ≥ 26.5 µmol/L within 48h or ≥ 1.5 times baseline within the last 7 days or urine output < 0,5 ml/kg/h for 6 hours
- ICU admission (and date of discharge if happens)
- Oxygen requirement: date of beginning and cessation
- Mechanical ventilation (non-invasive or invasive): date of beginning and cessation
- Acute respiratory distress syndrome, as define by the Berlin criteria (46): acute lung injury ≤ 1 week, bilateral opacities consistent on chest imaging not fully explained by other lung pathology, heart failure or volume overload, PaO2/FiO_2 ratio ≤ 300mmHg with a minimum of 5 cm H_2O PEEP (or CPAP)
- Shock requiring vasopressors
- Extracorporeal membrane oxygenation (ECMO): date of beginning and cessation
- Renal replacement therapy: date of beginning and cessation
- Biology: as mentioned at 5.1, according to the physician's decision

5.3 End of study visit (visit or phone call at day 28 ± 4 days)

- All patients still hospitalized at day 28, will have a visit with an events collection as mentioned at 5.2.
- All survivors' patients already discharged from hospital will have a phone call by an investigator (physician) at day 28 (± 4 days) to collect the events occurred since discharge from hospital:
    - Clinical status on a seven-category ordinary scale (as defined above)
    - New hospitalization in a non-ICU
    - Cardiovascular death

- Non cardiovascular death and cause
- Myocardial infarction
- Myocarditis
- Stroke
- Heart failure; presence of congestive signs, IV use of diuretics
- Acute kidney injury, as defined in the KDIGO guidelines
- ICU admission
- Oxygen requirement: date of beginning and cessation
- Mechanical ventilation (non-invasive or invasive): date of beginning and cessation
- Acute respiratory distress syndrome, as define by the Berlin criteria
- Shock requiring vasopressors
- Extracorporeal membrane oxygenation (ECMO): date of beginning and cessation
- Renal replacement therapy: date of beginning and cessation

5.4 Expected length of participation and description of the chronology and duration of the study.

Duration of enrolment period:	1 month
The length of participation for participants, of which:	28 days (+/- 4 days)
Maximum period between screening and enrolment:	7 days
Treatment duration:	1 month
Duration of follow-up period:	1 month
Total study duration:	2 months

5.5 Table or diagram summarising the chronology of the study

Actions	D0 (Baseline visit)	Every day (D1-28, discharge or death)	End of study: day 28 (+/- 4 days)
Information	X		
Informed consent	X		
Verification of inclusion and exclusion criteria	X		
History	X		
Clinical examination	X	X	X (if still hospitalized)
Clinical status on a seven-category ordinary scale	X	X	X
Tests (biochemistry, hematology, etc.)	X	X (at physician's discretion)	X (if still hospitalized)
Dispensation of treatments	X	X	X (if still hospitalized)
Compliance	X	X	X

Adverse events	X	X	X (by phone call if patients already discharged)

5.6 Distinction between standard care and study

TABLE: "Standard care" vs. "additional interventions" required specifically for the study

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with <u>standard care</u>**	**Interventions, procedures and treatments added for <u>research purposes</u>**
Treatments	RAS blockers continuation, calcium channel blockers or other antihypertensive drugs, diuretics, nitrates antibiotics, remdesivir, lopinavir-ritonavir, tocilizumab, azithromycin, chloroquine, hydroxychloroquine	RAS blocker discontinuation
Visits	Daily visit during hospitalization	Phone call at day 28
Blood samples	complete blood count, creatinine, blood urea nitrogen, potassium, sodium, bicarbonate, alanine/aspartate aminotransferase, bilirubin, albumin, lactate dehydrogenase, prothrombin time, activated partial thromboplastin time, D-dimers, troponin I us, creatine kinase, natriuretic peptides (BNP or Nt-proBNP), C-reactive protein, procalcitonin, ferritin, arterial blood gas with lactate, viral load of SARS Cov 2 (blood)	None
Imaging	Chest X-ray, CT-chest, echocardiography or cardiac MRI if indicated	None

6 <u>ELIGIBILITY CRITERIA</u>

6.1 Inclusion criteria

1. Age ≥ 18 year/old
2. Chronically treated with RAS blockers: ACE inhibitors or ARBs on the last prescription prior to admission and treatment duration ≥ 1 month
3. Diagnosis of COVID-19, confirmed by the presence of SARS-CoV2 on any biological sample with any detection method
4. Patients hospitalized
5. Negative pregnancy test at inclusion visit for women of childbearing potential
6. Women of childbearing potential must agree to use adequate contraception according to Recommendations related to contraception and pregnancy testing in clinical trials, by Clinical Trial Facilitation Group (CTFG)

6.2 Exclusion criteria

1. Shock requiring vasoactive agents
2. Acute respiratory distress syndrome requiring invasive mechanical ventilation
3. Circulatory assistance
4. History of malignant hypertension according to the definition of the 2018 ESC/ESH guidelines on hypertension : severe hypertension associated with funduscopic changes (flame hemorrhages and/or papilledema), microangiopathy, and disseminated intravascular coagulation (47)
5. Uncontrolled blood pressure despite the use of five antihypertensive drugs
6. History of nephrotic syndrome
7. History of hospitalization for hemorrhagic stroke in the past 3 months
8. RAS blockers therapy previously stopped > 48h
9. Pregnancy, breastfeeding
10. No affiliation to the French Health Care System “Sécurité Sociale”
11. Inability to obtain informed consent

6.3 Recruitment procedure

Patients will be recruited in hospitalization.
Considering the high number of patients infected with SARS-CoV2 in Italy, we believe that the number of patients infected with SARS-CoV2 in France can be similar and that enrolling 554 patients in 12 centers is highly feasible (47 patients/months/center).

	Number of participants
Total number of participants to be included	554
Number of centers	12

Enrolment period (months)	1
Number of participants/centre	47
Number of participants/centre/month	**47**

6.4 Termination rules

6.4.1 Criteria and procedures for prematurely terminating the study treatment

Several situations are possible

- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form (CRF)
- Premature discontinuation of treatment, but the participant remains enrolled in the study until the end of their participation
- Premature discontinuation of treatment and withdrawal from the study

The investigator must:

- Document the reason(s)
- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant for 28 days ± 4 days. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse event will be monitored until it is resolved. As a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

6.4.2 Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- If, during the course of his/her participation in the study, the participant presents one of the following exclusion criteria, then the study product/procedure must be discontinued but the participant will continue to be monitored for the study.
- The investigator can permanently withdraw a participant from the study in case of consent withdrawal.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

If a participant withdraws consent, any data collected prior to the date of premature exit may still be used.

- If a participant exits the study prematurely, and if the participant agrees, state the procedure and schedule for collecting the data required by the protocol (primary endpoint, secondary endpoints, safety assessment)
- In case of withdrawal consent, patient's care will be done according to investigator decision.
- In case of serious adverse events, see the corresponding section on vigilance

6.4.3 Follow-up of participants following premature withdrawal from the study

If a participant discontinues the study, this will in no way affect their usual care for their condition.

6.4.4 Full or partial discontinuation of the study

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely discontinue all or part of the study, temporarily or permanently, in the following situations:

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms if there is a discrepancy in the serious adverse reactions between the treatment arms, requiring a reassessment of the benefit-risk ratio for the study.
- if an interim analysis confirms the efficacy of one of the treatment arms or, alternatively, the lack of efficacy.

Similarly, AP-HP, as the sponsor, or the Competent Authority (ANSM) may decide to prematurely discontinue the study due to unforeseen issues or new information about the product, in light of which the objectives of the study or clinical programme are unlikely to be achieved.

AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee) within a period of 15 days.

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

This study is a study without any added treatment.
Patients included in the study are already chronically treated by a RAS blockers.
The ACORES-2 trial will stop RAS blockers in one arm of the patients.
Therefore, there is no administrated treatment in this research.

7.1 Description of the experimental group

The experimental group, including 277 COVID-19 patients with chronic RAS blockers treatment will undergo withdrawal of their RAS blockers treatment. The treatment discontinuation will be tracked into the patient file.*

7.2 Description of the non-experimental group

The non-experimental group, including 277 COVID-19 patients with chronic RAS blockers treatment will continue their usual RAS blockers treatment without modification. Prescription of intakes will be kept into the patient file.*

*With respect to the epidemic context, all traceability will be insure with current care patient documents

7.3 Authorized and prohibited treatments (medicinal, additional medicinal, surgical), including rescue medications

Treatments interacting with the renin-angiotension system (other ACE inhibitors or ARBs than the usual patients' treatment) are prohibited.

- For all patients randomized in the discontinuation group, an alternative treatment will be proposed according to the appropriate guidelines of the European Society of Cardiology (hypertension, heart failure, coronary artery disease) and the tolerance of the patient
- In particular :
- in individuals at risk of uncontrolled blood pressure: consider Calcium Chanel blocker as a first line option, if necessary other antihypertensive drug (non-RAS blockers) can be added according to the physician decision
- In individuals with history of heart failure: consider adding diuretics and nitrates (oral or IV according to the physician decision)

Other drugs indicated for heart failure or hypertension such as calcium channel blockers, diuretics, beta blockers, central acting agents, nitrates are authorized with medical prescription.
Specific clinical (e.g.: blood pressure/Signs of heart failure) or biological (e.g.: creatinin, electrolytes), follow-up for each drug used as a replacement therapy in the group "discontinuation" will be performed according to the drug registration notice (RCP) of each drug
For woman of childbearing age, initiation or following of a contraception is needed to be included in the study.

8 EFFICACY ASSESSMENT

8.1 Description of efficacy endpoints assessment parameters

The individual endpoints will be defined as follows.

8.1.1 Death

- **Any death**: death from any cause

- **CV death**: any death with a clear relationship to underlying coronary heart disease (including death secondary to acute MI, sudden death, unobserved and unexpected death, resuscitated out-of hospital cardiac arrest that does not survive to hospital discharge), stroke, and other death that cannot definitely be attributed to a non-CV cause.

8.1.2 Myocardial infarction

The definition of MI is based on the new Fourth Universal Definition of Myocardial Infarction written by Thygesen et al on behalf of the Joint ESC/American College of Cardiology Foundation (ACCF)/AHA/World Health Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction (48).
ACORES-2 will consider only **spontaneous MI**, excluding MI type 3 (fatal), which will be captured separately as death.

MI Type 1: Spontaneous MI: Symptoms of myocardial ischemia, new ischemic changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic etiology, identification of a coronary thrombus by angiography or autopsy.

MI Type 2: Secondary MI: Symptoms of myocardial ischemia, new ischemic changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic etiology, evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis.

8.1.3 Myocarditis

An acute myocarditis is defined as an event that meets the following criteria (49):

a. Clinical presentations:
   - Acute chest pain, pericarditic, or pseudo-ischemic
   - New-onset (days up to 3 months) or worsening of: dyspnea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
   - Subacute/chronic (3 months) or worsening of: dyspnea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
   - Palpitation, and/or unexplained arrhythmia symptoms and/or syncope, and/or aborted sudden cardiac death
   - Unexplained cardiogenic shock

b. Diagnostic criteria
   - ECG/Holter/stress test features:
     - Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS

complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia

- Myocardiocytolysis markers Elevated TnT/TnI
- Functional and structural abnormalities on cardiac imaging (echo/angio/CMR)
    - New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi
- Tissue characterization by CMR (2018 Lake Louise criteria) (50):
    - main criteria:
        - myocardial edema: T2 mapping or T2STIR
        - non-ischemic myocardial injury: abnormal T1, ECV (extracellular volume) or LGE (late-gadolinium enhancement)
    - supportive criteria:
        - pericarditis: effusion in cine images or abnormal LGE, T2 or T1
        - systolic left ventricular dysfunction: regional or global wall motion abnormality

A myocarditis is clinically suspected in the presence of ≥1 clinical presentation and ≥1 diagnostic criterion from different categories, and in the absence of:

1. angiographically detectable coronary artery disease (coronary stenosis ≥ 50%);
2. known pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g. valve disease, congenital heart disease, hyperthyroidism, etc.)

8.1.4 Stroke

Any stroke is defined as the presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting more than 24 hours. It is strongly recommended (but not required) that an imaging procedure such as a Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI) will be performed.
Both ischemic and hemorrhagic stroke will be considered as an endpoint and adjudication will have to differentiate the 2 types of events.
Diagnosis of stroke is based on clinical presentation (signs), duration and confirmatory investigations as follows:

- Clinical Presentation (At least 1 new neurological sign):

Hemiplegia, Hemianesthesia, Hemiparesis, Dysphasia, Vertigo, Diplopia, Dysphagia, Loss of vision on one side; Amaurosis fugax; Global amnesia; Bilateral or alternating weakness or sensory symptoms; Sensory loss; Dysarthria; Ataxia; Drop attacks; Another neurological sign

Duration (must be either ≥ 24 hours or ≤ 24 hours because of a pharmacologic or non-pharmacologic intervention).

- Confirmatory Investigations (At least 1):

Neurologist evaluation; Brain image study or procedure (CT-scan; MRI ± magnetic resonance angiography; Cerebral vessel angiography)

Stroke will be classified as follows:

1. <u>Transient ischemic attack</u>

TIA is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction

2. <u>Stroke</u>

Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

Classification:

A. Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

B. Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

C. Undetermined Stroke

Undetermined stroke is defined as a stroke with insufficient information to allow categorization as A or B.

8.1.5 Heart failure

An episode of HF is defined as an event that meets the following criteria:

a. for patients already discharged from the hospital: unplanned admission to an inpatient unit or an unplanned visit to the cardiologist or an emergency department

AND

b. Clinical symptoms of heart failure, including at least one of the following new or worsening

- dyspnea
- orthopnea
- paroxysmal nocturnal dyspnea
- increasing fatigue/worsening exercise tolerance

AND

c. Physical signs of heart failure, including at least two of the following:

- edema (greater than 2+ lower extremity)
- pulmonary crackles greater than basilar (pulmonary edema must be sufficient to cause tachypnoea and distress not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure)
- jugular venous distension
- tachypnoea (respiratory rate > 20 breaths/minute)
- rapid weight gain
- S3 gallop
- increasing abdominal distension or ascites
- hepatojugular reflux
- radiological evidence of worsening heart failure
- A right heart catheterization within 24 hours of admission showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mm Hg or a cardiac output < 2.2 L/min/m2

NOTE:
Biomarker results (e.g., brain natriuretic peptide (BNP)) consistent with congestive heart failure will be supportive of this diagnosis, but the elevation in BNP cannot be due to other conditions such as cor pulmonale, pulmonary embolus, primary pulmonary hypertension, or congenital heart disease. Increasing levels of BNP, although not exceeding the ULN, may also be supportive of the diagnosis of congestive heart failure in selected cases (e.g. morbid obesity).
Echocardiographic abnormalities such as a reduction in LVEF ≥ 5%, increased left ventricular filling pressure or a dilated inferior vena cava should be documented (recommendation, not mandatory) to support the diagnosis of heart failure.

AND

d. Need for additional/increased therapy defined by:

- Initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving

- maximal therapy for heart failure and including at least one of the following:
  - Initiation of or a significant augmentation in oral therapy for the treatment of congestive heart failure
  - Initiation of intravenous diuretic, inotrope, or vasodilator therapy

- Up titration of intravenous therapy, if already on therapy
- Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure.

AND

e. No other non-cardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms is identified.

NOTE: It is recognized that some patients may have multiple simultaneous disease processes. Nevertheless, for the end point event of heart failure requiring hospitalization, the diagnosis of congestive heart failure would need to be the primary disease process accounting for the above signs and symptoms.

8.1.6 Acute kidney injury

Acute kidney injury is defined by the KDIGO Guidelines as follows (45):

- increase in serum creatinine ≥ 26.5 µmol/L within 48h
- or increase in serum creatinine ≥ 1.5 times baseline within the last 7 days
- or urine output < 0,5 ml/kg/h for 6 hours

Its severity is staged according to the following criteria:

- stage 1:
  - increase in serum creatinine ≥ 26.5 µmol/L within 48h
  - or increase in serum creatinine ≥ 1.5 times baseline within the last 7 days
  - or urine output < 0.5 ml/kg/h for 6 hours
- stage 2:
  - increase in serum creatinine 2-2.9 times baseline
  - or urine output < 0.5 ml/kg/h for ≥ 12 hours
- stage 3:
  - increase in serum creatinine ≥ 353.6 µmol/L
  - or increase in serum creatinine ≥ 3 times baseline
  - or initiation of renal replacement therapy
  - or urine output < 0.3 ml/kg/h for ≥ 24 hours
  - or anuria ≥ 12 hours

8.1.7 Acute respiratory distress syndrome (ARDS)

ARDS is defined by the Berlin definition (46) as the association of the following criteria:

- acute lung injury ≤ 1 week of a known clinical insult or new worsening respiratory symptoms
- chest imaging (X-ray or CT) showing bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules

- respiratory failure not fully explained by cardiac failure or fluid overload
- PaO_2/FiO_2 ratio ≤ 300mmHg with a minimum of 5 cm H_2O PEEP (or CPAP)

8.1.8 Shock requiring vasopressors

A. Cardiogenic shock

Cardiogenic shock is defined as follow, based on the basis of the and the CULPRIT-SHOCK Study (51,52).

- Systolic blood pressure < 90 mmHg for > 30 min
- Or catecholamines required to maintain pressure > 90 mmHg during systole
- Signs of pulmonary congestion
- Signs of impaired organ perfusion with at least one of the following criteria
  - Altered mental status
  - Cold, clammy skin and extremities
  - Oliguria with urine output < 30 ml/h
  - Lactate > 2.0 mmol/l

B. Septic shock

Septic shock is defined as described in the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (53) by the association of:

- Sepsis:
  - life-threatening organ dysfunction: acute change in total SOFA score ≥ 2 points consequent to the infection
  - caused by a dysregulated host response to infection.
- persisting hypotension requiring vasopressors to maintain mean arterial pressure ≥ 65 mm Hg
- serum lactate level > 2 mmol/L despite adequate volume resuscitation

8.2 Anticipated methods and timetable for measuring, collecting and analyzing the efficacy data

The parameters for assessing efficacy were collected according to the schedule in table paragraph 5.5.

9 SPECIFIC STUDY COMMITTEES

9.1 Steering Committee

The Steering Committee is composed of the principal investigator, the scientific director and members selected on the basis of outstanding expertise in the field and contribution to the study, one statistician and one sponsor (AP-HP) representative.
The Steering Committee is in charge of monitoring all activities towards the objective of the project in order to deliver as promised, in due time and in the budget. The Steering Committee shall thus:
· Control the execution of the project with regards to the project schedule and the description of work annexed to the protocol and to monitor corrective actions;
· Propose all significant modifications of the work plan or the protocol
The DRCI sponsor retains decision-making authority.

10 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

10.1 Description of Safety endpoints assessment parameters

There are no specific research protocol related-risks in ACORES-2 trial.
No invasive procedure is planned.
The only identified potential risks are related to withdrawal of RAS blockers which is evaluated by the primary safety endpoint of the trial.

10.2 Anticipated methods and timetable for measuring, collecting and analyzing the safety endpoints

The safety assessment shall be done by collecting all adverse events that occur during the research, all events shall be graded. Adverse events shall be collected according to the schedule in table of paragraph 5.5 of the protocol.

10.3 Recording and reporting adverse events

10.3.1 Definitions

According to Article R.1123-46 of the *Code de la Santé Publique* (French Public Health Code):

- **Adverse event**

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study or with the product subject to the study.

- **Adverse reaction**

An adverse event occurring in a study involving human participants when this event is related to the study or to the product being studied.

- **Adverse reaction to an investigational medicinal product**

Any untoward and unwanted reaction to an investigational medication regardless of the dose administered.

- **Serious adverse event or reaction**

Any adverse event or reaction that results in death, threatens the life of the participant enrolled in the study, requires hospitalization prolongs existing hospitalization, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity, and in the case of a medication, regardless of the dose administered.

- **Unexpected adverse reaction in the experimental arm**

Any adverse reaction related to the discontinuation whose nature, severity, frequency or outcome is inconsistent with the standard safety information described in the summary of the product characteristics, or in the investigator's brochure if the product is not authorized.

<u>According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for sponsors of clinical trials (ANSM)</u>:

- **Emerging safety issue**

Any new information that may lead to a reassessment of the risk/benefit ratio of the trial or of the product under investigation, modifications in the investigational medicinal product use, the conduct of the clinical trial or the clinical trial documents, or a suspension, interruption or modification of the clinical trial or of similar trials.
For studies involving the first administration of a health product in healthy volunteers: any serious adverse reaction.
Examples:
a) any clinically significant increase in the frequency of an expected serious adverse reaction;
b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial which have been notified to by the investigator to the sponsor, as well as potential follow-up reports;
c) any new fact relating to the conduct of the clinical trial or the development of the investigational medicinal product, if the new fact is likely to affect participant safety
Examples:

- a serious adverse event likely to be related to the trial's interventions and diagnostic procedures and which may impact the conduct of the clinical trial,
- a significant risk for the trial participants such as a lack of efficacy of the investigational medicinal product used in the treatment of a life-threatening disease,
- significant safety results from a recently completed study on animal subjects (such as a carcinogenicity study),
- the premature termination, or temporary suspension, of a trial conducted with the same investigational medicinal product in another country, for safety reasons
- an unexpected serious adverse reaction related to a non-investigational medicinal product required to conduct the trial, (e.g.: "challenge agents", rescue treatment)

d) recommendations from the Data Safety Monitoring Board (DSMB), if they are relevant to the safety of the participants
e) any unexpected serious adverse reaction reported to the sponsor by another sponsor of a clinical trial carried out in a different country but relating to the same medication

10.3.2 The role of the investigator

The investigator must **assess the seriousness of each adverse event** and record all serious and non-serious adverse events in the case report form (CRF).
The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the intensity** of the adverse events:
- by using the CTCAE scale

The investigator must **assess the causal relationship** between serious adverse events and the investigational strategy added by the study.

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following 4 causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not excluded)

Their definition is presented in the following table (excerpt from WHO-UMC causality categories, version dated 17/04/2012).

Table: WHO-UMC causality categories (excerpt)

Causality term	Assessment criteria*
Certain to occur	· Event or laboratory test abnormality, with plausible time relationship to drug intake** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable/Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with
**Or study procedures

10.3.2.1 Serious adverse events that require the investigator to notify the sponsor without delay

As per article R.1123-49 of the *Code de la Santé Publique* (French Public Health Code), the investigator notifies the sponsor without delay on the day the investigator becomes aware of any serious adverse event which occurs during a study that meets the description in line 1° of Article L.1121-1 of the Code de la Santé Publique**, with the exception of any event which is listed in the protocol** and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening to the participant enrolled in the study (for this protocol, see exceptions listed on paragraph 10.3.2.2.2)
3- requires hospitalization or prolongation of existing hospitalization (see exceptions listed on paragraph 10.3.2.2.2)
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

10.3.2.2 Specific features of the protocol

10.3.2.2.1 Other events that require the investigator to notify without delay the sponsor

- Adverse events deemed "medically significant"

The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

- acute heart failure grade 4 and 5 according to CTCAE scale (not related to COVID 19)
- myocardial infarction grade 4 and 5 according to CTCAE scale,
- myocarditis grade 4 and 5 according to CTCAE scale,
- cardiogenic shock with requirement of vasopressors or a circulatory assistance (not related to COVID 19 according to investigator),
- stroke 4 and 5 according to CTCAE scale,
- Hypertension grade 4 and 5 according to CTCAE scale.
- Acute Kidney Injury, requiring renal replacement therapy, grade 4 and 5 according to CTCAE scale

Grade 4 correspond to life threatening and grade 5 correspond to fatal outcome

- ***In utero* exposure**

The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.
If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.

- Exposure **while breastfeeding**

Exposure while breastfeeding occurs if an infant or a child may have been exposed to a medicinal product *via* the breast milk of a mother being treated with an investigational medicinal product.
Even if it is not associated with an adverse event, the investigator must notify the sponsor without delay on the day the investigator becomes aware of the exposure while breastfeeding.

10.3.2.2.2 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are only recorded in the case report forms (CRF).

- *Normal and natural course of the condition*:

- **Re-Hospitalisation** for any reason (including CV reasons) except those described in the Adverse events deemed "medically significant" paragraph
- **Admission to an intensive-care unit** except those described in the Adverse events deemed "medically significant" paragraph
- **Acute cardiac injury:** acute heart failure, type 1 or 2 myocardial infarction, myocarditis, except those described in the Adverse events deemed "medically significant" paragraph
- **Acute kidney injury**, except grade 4 and 5 according CTCAE scale or requiring renal replacement therapy
- **Acute respiratory distress syndrome**, requirement of mechanical ventilation (invasive or not) or an ECMO
- **Multiple organ failure** except grade 5 according CTCAE scale.

The primary objective of the study is to compare the effect of discontinuation versus continuation of RAS blockers on the clinical course of patients with confirmed COVID-19 infection leading to hospitalization
The mortality rate linked to the studied condition of COVID-19 is 22% at 28 day (3).
The interventions added by the study being Continuation or Discontinuation of RAS blockers in context of pandemic of COVID-19, all serious adverse event ≤ grade "3 (and except those described in the Adverse events deemed "medically significant" paragraph) do not need to be notified to the sponsor without delay but will be recorded in the case report forms.
Retrieval of all serious adverse event from the case report forms will be carried out by clinical research unit as often as necessary.
The retrieval of all serious adverse event data will be sent by the clinical research unit to the vigilance department at expertisecsi.drc@aphp.fr and to the members of the Data Safety Monitoring Board before each meeting of the DSMB.

If there is any discrepancy between the groups or if the mortality rate is higher than expected, affecting participants safety and which require the sponsor to take urgent safety measures, the ANSM (French Health Products Safety Agency) will be informed about the emerging safety issue without delay.

- *Special circumstances*

- **Hospitalisation** for a known pathology
- **Hospitalisation** for medical treatment or surgery scheduled before the research

All serious adverse reaction described in the SMPC of the treatments (RAS blockers, Calcium Chanel blocker, other antihypertensive drug (non-RAS blockers), diuretics and nitrates (oral or IV) **do not need to be notified to the sponsor without delay but will be recorded in the case report forms.**

The investigator must report these adverse reactions to the relevant regional pharmacovigilance center, Centre Régional de Pharmacovigilance (CRPV).

Common side effects associated with RAS blockers (which could be serious) include:

- hyperkaliemia
- headaches, dizziness
- hypotension, syncope
- irritative cough, bronchitis, sinusitis, dyspnea
- digestive disorders, abdominal discomfort, dyspepsia, diarrhea, nausea and vomiting
- rash
- muscular spasms
- fatigue, chest pain

Less common side effects include:

- neutropenia, agranulocytosis, anemia, thrombopenia
- confusion
- tremor, vertigo
- conjunctivitis
- tinnitus, hearing disorder
- vascular stenosis, vasculitis
- glossitis
- cholestatic jaundice
- exfoliative dermatitis
- asthenia

10.3.2.3 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:

- from the date on which the participant signs the consent form
- throughout the whole follow-up period required for the trial 28 days± 4 days

- indefinitely, if the SAE is likely to be due to the investigational medicinal product or to the study interventions (e.g. serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities)

10.3.2.4 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be non-identifying. In addition, the documents must include the following: study acronym, number and participant's initials.

Any adverse event will be monitored until fully resolved (stabilization at a level considered acceptable by the investigator or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Safety Department can be contacted via email: vigilance.drc@aphp.fr.

10.3.3 Role of the sponsor

The sponsor, represented by its Safety Department, shall continuously, throughout the trial, assess the safety of each investigational medicinal product throughout the study.

10.3.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all the adverse events reported
- the **causal relationship** between these events and each investigational medical procedure added by the study and any other treatments,

All serious adverse events which the investigator and/or the sponsor reasonably believe may have a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.

- the **expected or unexpected nature** of the serious adverse reactions
  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorized, is considered unexpected.
  The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational product(s): RAS blockers

- refer to the SmPC of the used products, in force at the time of SAE receipt.

❖ The serious adverse events potentially related to the interventions, specific to the study are, and related to discontinuation of RAS blockers:

- Increase of cardiovascular events, such as acute heart failure, uncontrolled hypertension, myocardial infarction or stroke, myocarditis, cardiogenic shock with requirement of vasopressors or a circulatory assistance,
- More COVID-19 related cardiac injuries, such as acute cardiac injury or myocarditis
- More acute lung injuries

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM:

- The sponsor must send the initial report without delay upon learning of the unexpected serious adverse reaction if is fatal or life-threatening, or otherwise within 15 days from learning of any other type of unexpected serious adverse reaction;
- All additional, relevant information must be declared by the sponsor in the form of follow-up reports within a period of 8 calendar days starting from when the sponsor had this information.

Any suspected unexpected serious adverse reaction must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).
The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the research participants.

10.3.3.2 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials. For trials involving the first administration or use of a health product in healthy volunteers: any serious adverse reaction.

The sponsor will inform the competent authority and the Research Ethics Committee without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

10.3.3.3 Annual safety report

Special case of short-term clinical trials:
If the duration of the clinical trial is less than one year, the promoter does not have to establish an annual safety report.
However, if several short-term clinical trials have been carried out during this same period, it is recommended to submit an annual safety report to the Member States concerned, which allows an evaluation of comprehensive information on the safety of the investigational medicinal product.

10.3.4 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) may be established by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The sponsor is responsible for justifying the creation or absence of such a committee to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee).

A DSMB will be established for this trial. The DSMB must hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the competent authority and the CPP (Research Ethics Committee).
All missions as well as the specific operating procedures of the DSMB are described in the study's DSMB charter.

The DSMB members are:
- List the members of the DSMB → Pr Guillaume Cayla (cardiology, CHU Nimes), Pr Jean Chastre (intensive-care medicine, Pitié-Salpêtrière hospital, Paris), Michel Cucherat (clinical pharmacology, Hospices Civils, Lyon)
The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.

11 DATA MANAGEMENT

11.1 Data collection procedures

All information required by the protocol must be provided in the case report form and given by the investigator for each missing explanation. The data will be transferred in the case report form as and when they are obtained.

11.2 Identification of data recorded directly in the CRFs which will be considered as source data

All data will be recorded first in the medical file.

11.3 Right to access data and source documents

11.3.1 Data access

In accordance with GCPs:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- the investigators will ensure the persons in charge of monitoring, quality control and auditing or inspecting the interventional study involving human participants have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.3.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file (the medical file contains original biological examination results, summary from imaging examinations, etc.)

11.3.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the *Code de la Santé Publique* [French Public Health Code]) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the *Code Pénal* [French Criminal Code]).

During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialized collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown. Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.4 Data processing and storage of research documents and data

11.4.1 Identification of the data processing manager and location(s)

All subject data generated during the study will be recorded in a paper CRF.
Only the investigator and co-workers authorized by him (as listed on the specific form provided by the Sponsor) will be allowed to entered data or to make corrections in the paper CRF. At the end of the study each eCRF will be signed and dated by the investigator and archived.
During the study, all data will be recorded by a central team from paper CRF in the electronic Case Report Form (eCRF) provided by the Sponsor: web-based electronic support. eCRF will be specifically designed to meet the data recording requirements of the Clinical Study Protocol.
Statistical analysis will be conducting by Unité de Recherche Clinique Lariboisière-Saint Louis under the responsibility of Pr Eric Vicaut.

11.4.2 Data entry

Data entry will be performed by investigators and co-workers authorized by him by specially trained staff in non-identifying case report forms.

11.5 Data ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

12 STATISTICAL ASPECTS

12.1 Statistical Design / Model

ACORES-2 will be a phase III national, multicenter, comparative, controlled, randomized, open label trial in parallel groups among patients hospitalized for COVID-19 and treated with RAS blockers. It will test the superiority of the "discontinuation strategy" versus the "continuation strategy". Participants will be distributed in a 1:1 ratio between the 2 groups.

12.2 Null and Alternative Hypotheses

The primary aim of the trial is to demonstrate difference in time to clinical improvement (T) between discontinuation strategy vs the “continuation strategy”
The null and alternative hypotheses are as follows:
H_0: $T_{discontiuation} = T_{contiuation}$
versus
H_1: $T_{discontiuation} \neq T_{contiuation}$

12.3 Planned Analyses

12.3.1 Populations to be analysed

The main analysis will be based on the intent-to-treat population (ITT) of all patients randomised (irrespective of which study treatment is given or if any study treatment is adequately received). Per protocol analysis (PP) of all patients randomized & treated without major protocol violations/deviations will be considered as secondary.

12.3.2 Patient accountability

Disposition of patients, patient status and patients excluded from PP populations will be summarised by treatment group. Descriptive statistics for primary reason for patient’s withdrawal will be also presented by treatment group as well as a list of these patients sorted by treatment group.
Reasons for drop-outs in each treatment group will be displayed. A detailed list of drop-out patients will also be provided.

12.3.3 Baseline characteristics

Baseline characteristics will be tabulated and comparability / differences between the treatment groups will be examined by means of descriptive statistics. As recommended by CONSORT no tests will be carried on baseline variables.

12.3.4 Interim analyses

Interim analyses will be carried out after 33% and 66% of inclusion. They will allow early rejection of the null hypothesis for efficacy. We will use the O'Brien-Fleming spending function to determine the test boundaries. In addition a blinded sample size reassessment procedure will be performed at the second interim analysis that would allow the data safety monitoring board to recommend, if required, an increase of the sample size to reach the expected power.

12.4 Efficacy Analysis

12.4.1 Main Efficacy Criterion

The primary ITT analysis on the primary endpoint will be carried out by Cox model of survival analysis. Possible interaction between treatment and strata will be tested. The corresponding 95% confidence interval of Hazard ratio will be calculated from Cox model.

12.4.2 Secondary Efficacy Criteria

If a significant difference is found for the main criterion, The secondary criteria will be tested using a hierarchical procedure in the following order:

1. Clinical status as assessed with the seven-category ordinal scale on days 28.
3. Number of days alive free of oxygen.
4. Number of days alive outside hospital during 28 days after randomization.
5. Number of days alive free of intensive-care unit (ICU) admission or mechanical ventilation (invasive or non-invasive) 28 days after randomization.
6. Number of days alive free of mechanical ventilation (invasive or non-invasive) 28 days after randomization.
7. Number of days alive free of ICU admission 28 days after randomization.
8. Rate of all-cause mortality at day 28.
9. Rate of cardiovascular death at day 28.
10. Number of days alive free of acute kidney injury during hospitalization.

Secondary criteria will be compared using Mann-Whitney tests for quantitative variables and ordinal logistic regression to analyze the seven-category ordinal. Chi-square tests for categorical data and Cox survival analysis for time to event. Tests will be performed at a two-sided 5% significant level for one criterion only if a significant difference has been found for the previous criterion in the list.
Differences in medians between groups will be reported with associated 95% CI

12.5 Safety Analysis

(Serious) adverse events will be tabulated per treatment group.
All (dichotomized) endpoints will be analyzed by chi-square test on proportions and the 95% confidence interval on the odds-ratio will be presented..

12.6 Handling of missing data

Very few missing data are expected for the main criterion. In the intent-to-treat analysis missing data if present, will be replaced using multiple imputation technique.

12.7 Randomisation

The randomisation will be stratified by centre and status of cardiac insufficiency (present/absent).

12.8 Sample size issues

This trial is designed in a public health emergency context, at which time there is limited information about clinical outcomes in Covid-19 hospitalized patients.
We will include n=277 patients in each group to provide the trial with 90% power to detect a difference, at a two-sided global significance level of $\alpha = 0.05$, of 5 days in the median time to clinical improvement between the two groups, assuming that the median time in the standard-care group will be 16 days (B. Cao et al NEJM March 18th 2020). We considered 3 equally spaced analyses allowing early stopping for efficacy according to the O Brien-Fleming boundaries.
Considering around 25 % of patients in the cardiac insufficiency stratum, we also checked that, in case of significant interaction between stratum and treatment due to a minor effect of the
treatment in patients with cardiac insufficiency, this sample size will also allow 80% to detect a 5 days in the median time to clinical improvement in the other stratum that will include n=207 patients/group.
Primary efficacy analysis will be on an intention-to-treat basis and included all the patients who had undergone randomization.
The time to clinical improvement will be assess after day 28, and absence of clinical improvement or death before day 28 will be considered as right-censored at day 28.
The time to clinical improvement will be analyze by Kaplan-Meier method and compare with a log-rank test.
In addition a blinded sample size reassessment procedure will be performed at the second interim analysis that would allow the data safety monitoring board to recommend, if required, an increase of the sample size to reach the expected power.

12.9 Statistical Software and responsibility

All analyses will be made using SAS Software version 9.4 or R Packages under the responsibility of Pr Eric Vicaut.

13 QUALITY CONTROL AND ASSURANCE

Every research project involving human participants managed by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored interventional research involving human participants.

13.1 General organization

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centers.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits.
The purpose of monitoring the study, as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

13.1.1 Strategy for center opening

The strategy for opening the centers established for this study is determined using the appropriate monitoring plan. In the context of this pandemia, sites will be opened as fast as we can (by phone).

13.1.2 Scope of center monitoring

In the case of this D risk study the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study.

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: regarding the context of pandemia and quarantine, we will performed a phone call at the beginning of the study to remain reglementary procedures, and we will check informed consent as soon as possible

13.3 Case report forms

All information required by the protocol must be entered in the case report forms and an explanation must be given for all missing data. The data must be collected as and when they are obtained and must be clearly and legibly transcribed.

Any errors identified in the case report forms must be crossed out and the correct information entered next to the crossed-out data, together with the initials of the Investigator or authorized person who made the correction, the date and if necessary, the reason for the correction.

13.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsor's procedures.

13.5 Audits/inspections

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.
An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

13.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (*Répertoire Partagé des Professionnels de Santé*, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training.

Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.

The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing research participants and obtaining their consent

- ***Who is informed?*** *The participant*
- ***Who is providing consent?*** *The participant*
- ***When?*** *At Baseline*
- ***How?*** *Information note given to the participant and oral explanation*
- ***Who informs and obtains the consent?*** *The investigator, or* a physician representing the investigator

In accordance with Article L1122-1-1 of the Code de la Santé Publique (French Public Health Code), no interventional research involving human participants can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of the aforementioned Code.

A reflection period of **6 hours** is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person's freely given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study at Baseline (max 7 days after hospitalization).

A copy of the information notes and consent form signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

14.2 Prohibition from participating in another clinical study or exclusion period set after the study

Participants include in this study cannot be enrolled in any another interventional research protocol until completing the last visit of the ACORES 2 trial (day 28)".

Participants can participate to any observational study.

14.3 Authorization for the research location

The study will be carried out in treatment units on individuals presenting a clinical condition for which the units are specialized and who require interventions that are routinely performed at those units. Therefore, the research location does not require specific authorization.

14.4 Legal obligations

14.4.1 Role of the sponsor

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the *Code de la Santé Publique (French Public Health Code)*. Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

14.4.2 Request for approval from the CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants concerning a medicinal product for human use, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance within force legislation and regulatory requirements.

14.4.3 Request for authorization from ANSM

Prior to starting the study, AP-HP, as sponsor, must obtains authorization from the ANSM (French Health Products Safety Agency) for the interventional study involving human participants concerning a medicinal product for human use, within the scope of the ANSM's authority and in accordance within force legislation and regulatory requirements.

14.4.4 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

- Commitment to comply with "Reference Methodology" MR-001

This research is governed by the CNIL (French Data Protection Agency) "Reference Methodology for processing personal data used within the scope of health research" (amended MR-001). AP-HP, as sponsor of the research, has signed a declaration of compliance with this "Reference Methodology"

14.4.5 Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, approval from the CPP (Research Ethics Committee) and authorization from the ANSM within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

14.4.6 Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study.

14.4.7 Archiving

Specific documents for an interventional study involving human participants concerning a medicinal product for human use will be archived by the investigator and the sponsor for 15 years after the end of the research.
This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the center who participated in the study;
- A sealed envelope for the sponsor, containing a copy of all the information notes and consent forms signed by all individuals at the center who participated in the study;
- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list):
  - the successive versions of the protocol (identified by the version number and its date), and any appendices
  - the ANSM authorizations and CPP (Research Ethics Committee) decisions
  - any correspondence
  - the enrolment list or register
  - the appendices specific to the research
  - final study report
- The data collection documents

15 FUNDING AND INSURANCE

15.1 Funding sources

In progress

15.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article L.1121-10 of the *Code de la Santé Publique* (French Public Health Code).

16 PUBLICATION RULES

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and must name the sponsor AP-HP (DRCI), the ACTION Study Group and the source of funding, if funded by a call for tenders (e.g. national or regional PHRC); a copy of the publication must be sent to the sponsor (see below for rules governing affiliation, and naming of the sponsor and funders).
The scientific director and the coordinating investigator will be first and last author respectively. Members of the ACTION Study Group who drafted this protocol with the principal coordinating investigator and the scientific director will be listed as coauthor. Members of the steering committee will be listed as coauthors, Investigators will be listed according to the number of patients included in the protocol.

16.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
- The AP-HP institution must feature under the acronym **"AP-HP"** first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France

16.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

- "The sponsor was Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et à l'Innovation)"

16.3 Mention of the financial backer in the acknowledgements of the text

- If PHRC: “The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC COVID 2020 (French Ministry of Health)”

  OR

- If an AP-HP internal call for tenders, specify: “The study was funded by a grant from Assistance Publique – Hôpitaux de Paris”

This study has been registered on the website http://clinicaltrials.gov/ under number NCT04329195.

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