**Amiodarone or Verapamil in COVID-19 hospitalized patients with symptoms: Randomized clinical trial**

**The ReCOVery-SIRIO randomized study**

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# **1. Introduction**

Infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), also known as coronavirus disease (COVID-19), is currently classified by the World Health Organization (WHO) as an ongoing pandemic, with thousands of new cases diagnosed every day. In Italy COVID-19 is burdened with high mortality, probably due to the more advanced age and cardiovascular risk of the population. With no vaccine available, knowledge of effective available therapies is limited(1). Antiviral and antimalarial drugs are most commonly used to treat COVID-19, although these agents are not specific for SARS-CoV-2. Use of monoclonal antibodies appears promising, however they can influence course of the disease only in the latter inflammatory stage when cytokine storm occurs and clinical symptoms exacerbate. Notably, these antibodies do not affect the initial phase of COVID-19, i.e. penetration of SARS-CoV-2 into cells and viral replication. Therefore, there is an urgent need to seek pharmacological options to inhibit the initial stages of the infection (penetration and replication of the virus) using currently available drugs, which could be easily and promptly introduced into common clinical practice worldwide.

# **2. SARS-CoV-2 cell entry mechanism**

SARS-CoV-2 belongs to the family of *Coronaviridae*, which also includes Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). SARS-CoV-2 is highly contagious and is transmitted primarily via respiratory droplets. Coronavirus cell entry mechanism requires binding of viral spike protein (S protein) subunit S1 to angiotensin converting enzyme 2 (ACE2) receptors on human cells, and protein S priming by host proteases is responsible for fragmentation of this protein in S1/S2 location. S2 subunit is responsible for the fusion of viral envelope and host cell membrane. Transmembrane protease, serine 2 (TMPRSS2) is responsible for the cleavage of the open S protein of SARS-CoV-2 (2). Fusion with the host cell membrane(3) is possible thanks to S protein, which is calcium current-dependent. Modification of viral envelope with S protein exposure and fusion with host cell membrane, called endocytosis, constitutes the initial phase of cell entry and leads to replication of the virus (Fig. 1). The next crucial phase of cell entry is transportation of the virus in endocytic vesicles into endosomal space, where S protein is cleaved by cathepsin L, which promotes fusion of viral material with endosomal membranes. This process leads to the release of the viral genome into cytoplasm and subsequent replication of the virus (**Fig. 1**). These mechanisms of entry are shared by the new COVID-19 virus.

**Fig. 1.** SARS-CoV cell entry mechanism and potential role of calcium channel blockers.



# **3. Rationale for use of amiodarone and verapamil in patients with COVID-19.**

Amiodarone is an antiarrhythmic agent often used in patients with cardiovascular diseases. It has a complex mechanism of action, inhibiting different ion channels, including calciumchannels. Earlier studies have shown how amiodarone affects endosomal transport in SARS-CoV-infected cells by blocking calcium channels(4). It also has been reported that S protein undergoes calcium-dependent modulation. Therefore, we hypothesized that calcium-dependent mechanism exists, which allows interaction with the early stages of viral cell entry by conformational modifications of S protein. This hypothesis is clinically supported by recently published data showing that amiodarone, in concentrations obtained during antiarrhythmic therapy, inhibits cell entry by the virus (5). A similar effect was achieved with use of verapamil, a non–dihydropyridine calcium channel blocker, which exerts antihypertensive, antiarrhythmic and antianginal effects. Verapamil selectively inhibits intracellular transmembrane calcium flow through L-type voltage-dependent calcium channels. It should be underlined, that use of antiarrhythmic agents, such as amiodarone and verapamil, may also have additional beneficial effects due to the fact that up to 40% of COVID-19 patients requiring intensive care may develop arrhythmias related or not related to myocarditis. Moreover, fever that is present in 85% of COVID-19 cases, leads to tachycardia, and use of medications controlling heart rate may reduce the patient's discomfort.

# **4. The ReCOVery-SIRIO trial**

## **4. 1. General information**

A randomized study assessing amiodarone and verapamil compared with conventional therapy in the early, **symptomatic stage of infection in symptomatic patients with confirmed COVID-19**. The primary endpoint is clinical improvement. Follow up primary endpoint: 1-15 days. Assessments at day 7 and 28 or discharge will also be performed.

The study will be performed at around 7 sites in Poland, Italy, Spain and Canada.

A total of 804 Patients will be randomized into one of three study arms (**Fig. 2**):

1) administration of amiodarone (n=268);

2) administration of verapamil (n=268);

3) usual care (n=268).

**Fig. 2.** The ReCOVery-SIRIO study flow-chart.



**Perspectives of the ReCOVery-SIRIO trial**

Inhibition of viral replication and its potential for cell entry may have substantial influence on the clinical course of COVID-19 infection.

## **4.2 Study population – Inclusion Criteria**

1. Hospitalized patients with confirmed COVID-19 and symptoms. Confirmation of COVID-19 diagnosis should be made with Real-Time PCR (nasopharyngeal or oropharyngeal swabs, sputum, tracheal aspirates).
2. Written informed consent given prior to any trial-related procedure.
3. Male and female age 18 or more at the time of signing the informed consent.
4. An oxygenation index defined as quotient of partial pressure of oxygen in arterial blood (PaO2, in mmHg) and fraction of inspired oxygen (FiO2) > 200. It is recommended to measure partial pressure of oxygen (PaO2) using an arterial blood gas (ABG). Optionally, if arterial blood cannot be collected, the PaO2 level should be determined according to the table below (Table 1). Fraction of inspired oxygen (FiO2) for different oxygen therapy systems are given in Table 2.

**Table 1.** SpO2 to pO2 conversion

|  |  |
| --- | --- |
| **SpO2 [%]** | **pO2 [mmHg]** |
| 80 | 44 |
| 81 | 45 |
| 82 | 46 |
| 83 | 47 |
| 84 | 49 |
| 85 | 50 |
| 86 | 51 |
| 87 | 52 |
| 88 | 54 |
| 89 | 56 |
| 90 | 58 |
| 91 | 60 |
| 92 | 64 |
| 93 | 68 |
| 94 | 73 |
| 95 | 80 |
| 96 | 90 |
| 97 | 100 |
| 98 | 112 |
| 99 | 145 |

**Table 2.** Fraction of Inspired Oxygen (FiO2) for different methods of oxygen administration

|  |  |
| --- | --- |
| **Oxygen tank flow rate in liters/min** | **FiO2. Fraction of inspired Oxygen value** |
| **Nasal Cannula** |
| 0 | 0.21 |
| 1 | 0.24 |
| 2 | 0.28 |
| 3 | 0.32 |
| 4 | 0.36 |
| 5 | 0.40 |
| 6 | 0.44 |
| **Face mask** |
| 5 | 40 |
| 6-7 | 50 |
| 7-8 | 60 |
| **Face mask with reservoir** |
| 6 | 60 |
| 7 | 70 |
| 8 | 80 |
| 9 | 90 |
| 10 | 95 |

1. Willingness and ability to comply with the protocol.
2. Contraception and fertility:
3. **Female patients:**
	* must be of non-child-bearing potential i.e. surgically sterilized (hysterectomy, bilateral salpingectomy, bilateral oophorectomy at least 6 weeks before screening/enrolment) or post-menopausal (where postmenopausal is defined as no menses for 12 months without an alternative medical cause), or
	* if of child-bearing potential, must have a negative pregnancy test before the first IMP intake (blood / urine pregnancy test). They must agree not to attempt to become pregnant, must not donate ova, and must use a highly effective contraceptive method (see below) together with a barrier method during the clinical trial.
4. **Male patients** must agree not to father a child or to donate sperm starting at Screening, during the clinical trial. Male patients must also
	* abstain from sexual intercourse with a female partner (acceptable only if it is the patient’s usual form of birth control/lifestyle choice), or
	* use adequate barrier contraception during treatment with the IMP, and
	* if they have a female partner of childbearing potential, the partner should use a highly effective contraceptive method.
	* o if they have a pregnant partner, they must use condoms while taking the IMP to avoid exposure of the fetus to the IMP

**Highly effective methods of contraception meaning.**

Highly effective forms of birth control are those with a failure rate less than 1% per year and include:

− oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraceptives associated with inhibition of ovulation

− oral, injectable, or implantable progestogen-only hormonal contraceptives associated with inhibition of ovulation

− intrauterine device or intrauterine hormone-releasing system

− bilateral tubal occlusion

− vasectomized partner (i.e. the patient’s male partner underwent effective surgical sterilization before the female patient entered the clinical trial and is the sole sexual partner of the female patient during the clinical trial)

− sexual abstinence (acceptable only if it is the patient’s usual form of birth control/lifestyle choice; periodic abstinence [e.g. calendar, ovulation, symptothermal, postovulation methods] and withdrawal are no acceptable methods of contraception)

**Barrier methods of contraception include:**

− Condom (without spermicidal foam/gel/film/cream/suppository or fat- or oil-containing lubricants)

− Occlusive cap (diaphragm or cervical/vault caps) with spermicidal gel/film/cream/suppository.

## **4.3 Study population – Exclusion Criteria**

1. Acute respiratory distress syndrome (ARDS).
2. Contraindications for or known hypersensitivity to amiodarone or calcium channel blockers.
3. Long QT syndrome.
4. Prolonged baseline QTc interval (≥450 ms).
5. Cardiogenic shock or severe hypotension (< 90 mmHg).
6. Severe left ventricle dysfunction (left ventricular ejection fraction ≤35%).
7. Severe sinus - node dysfunction with marked sinus bradycardia.
8. 2nd/3rd degree heart block.
9. Bradycardia without pacemaker that has caused syncope**.**
10. History of severe dysthyroidism. Clinical signs and symtomps of thyroid disease if there are abnormal TSH and thyroxine (fT4)or triiodothyronine (fT3) levels in serum.
11. A-Fib/flutter conducted via accessory pathway (ie,Wolff -Parkinson-White).
12. Women who are pregnant or breastfeeding at study screening.
13. Patient with concurrent disease considered by the Investigator to be clinically significant in the context of the study.
14. Severe mental illness and/or a history or evidence of organic brain disease or dementia considered by the Investigator to be clinically significant in the context of the study, that would compromise the subject’s ability to comply with the study protocol.

# **5. Administration of IMP: amiodarone or verapamil**

## **5.1. Duration of therapy with amiodarone or verapamil**

It is strongly recommended that Investigational medicinal drugs IMP therapy should continue during hospitalisation: from day 1 until day 15 (14 full days). It means: amiodarone or verapamil will be administrated over 14 days (treatment from day 1, as soon as possible after COVID-19 diagnosis to day 15 of the study), unless there are emerging conditions requiring treatment interruption. However, if the patient's condition is good and allows discharge for the 14th day of hospitalization, the drug may be discontinued earlier.

The treatments can be continued beyond discharge if there is cardiovascular indication to prolong them.

## **5.2. Dosing of amiodarone and verapamil**

### 5.2.1 Amiodarone – Dose and Treatment Schedules

* Amiodarone should be administered orally in a daily dose of 200-400 mg (once or twice per day).
* Adjust dosage based on age, patient tolerance and cardiac response: Heart Rate, Blood Pressure, QT/QTc interval length, heart rhythm. Elderly (> 65 yrs): Initiate dosage at the lower end of the adult range.
* Therapy should continue until day 15 (14 full days) or more if there is cardiovascular indication to prolong them. If the patient is discharged home before the 14th day of hospitalization, treatment may be terminated earlier.

**Table 3**. Amiodarone. Dose and Treatment Schedule

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Treatment period** | **Procedure** | **Pharmaceutical form and route of administration** | **Dose of amiodarone** | **Frequency or/and Regimen** |
| **Day 1.****As soon as possible after randomization****to Day 15.1** | Oral administration | Tablets for oral use. | 200 mg | Once (200mg) or twice (2 x 200mg) per day.2,3 |

1 The treatment can be continued beyond discharge if there is cardiovascular indication to prolong them.

2 The IMT should be given in the maximum clinically tolerated dose.

Close monitoring with adjustment of dose as needed is essential. Maintenance dose should be determined according to patient tolerance as well as symptoms, cardiac response (Heart Rate, Blood Pressure, QT/QTc interval length, heart rhythm) and age. Elderly (>65yrs): Initiate dosage at the lower end of the adult range.

3 The IMT should be taken ones or twice per day at the same time daily**.**

### 5.2.2 Verapamil– Dose and Treatment Schedules

* Verapamil should be administered orally in a daily dose of 120-480 mg (3 or 4 devided doses).
* Adjust dosage based on age, patient tolerance and cardiac response: Heart Rate, Blood Pressure, QT/QTc interval length, heart rhythm). Elderly (>65 yrs): Initiate dosage at the lower end of the adult range.
* Therapy should continue until day 15 (14 full days) or more if there is cardiovascular indication to prolong them. If the patient is discharged home before the 14th day of hospitalization, treatment may be terminated earlier.

**Table 4.** Verapamil. Dose and Treatment Schedule

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Treatment period** | **Procedure** | **Pharmaceutical form and route of administration** | **Dose of verapamil** | **Frequency or/and Regimen** |
| **Day 1.****As soon as possible after randomization to Day 15.1** | Oral administration | Tablets for oral use. | 120-480mg2 | administered in 3 to 4 divided doses every 6-8 hours.3 |

1 The treatment can be continued beyond discharge if there is cardiovascular indication to prolong them.

2 The IMT should be given in the maximum clinically tolerated dose. The maximum IMT dose in this trial is 480mg of verapamil per day given orally in four divided doses. Close monitoring with adjustment of dose as needed is essential. Maintenance dose should be determined according to patient tolerance as well as symptoms, cardiac response (Heart Rate, Blood Pressure, QT/QTc interval length, heart rhythm) and age. Elderly (>65yrs): Initiate dosage at the lower end of the adult range.

3 The IMT should be taken at the same time daily.

## **5.3. Considerations for Use**

**It strongly recommended not to use antimalarial agents with amiodarone.**

**The daily monitoring of the heart rhythm and the QT interval length measurement in the three randomized arms is mandatory**. If a (corrected) QTc interval becomes prolonged > 500 ms in females, a reduction of the amiodarone dose is recommended.

If the interruption of the therapy occurs, evaluate drug re-challenge with closer monitoring if clinical conditions and ECG allow that.

If a marked bradycardia (ventricular rate <40 bpm) or severe hypotension (systolic blood pressure <90 mmHg) occur during treatment with amiodarone or verapamil, these treatments should be temporarily interrupted and then evaluate drug re-challenge with closer monitoring if clinical conditions allow that.

## **5.4. Other antiviral drugs**

During the study, it is not recommended to use other drugs with supposed and not scientifically documented antiviral activity, especially drugs not approved for use in COVID-19. However, it is possible to use these drugs if recommended by local guidelines.

Name of active ingredients and drug doses must be recorded in the eCRF.

## **5.5. Drug Interactions**

1. **Amiodarone**
* QT Prolonging Drugs (Class I and III antiarrhythmics, Fluoroquinolones, Macrolide antibiotics, Azole antifungals, Anti-malarial drugs): This drugs increase risk of Torsade de Pointes. Monitor QT interval.
* Protease-inhibitors (Ritonavir, Lopinavir): Protease inhibitors inhibit CYP3A4 to varying degrees and this leads to an increase in amiodarone concentrations. There was no evidence of toxicity.
* Negative Chronotropes (Digoxin, Beta-blockers, Verapamil, Diltiazem, Clonidine, Ivabradine): This drugs can potentiate the electrophysiologic and hemodynamic effects of Amiodarone, resulting in bradycardia, sinus arrest, and AV block. Monitor heart rate.
1. **Verapamil**
* Protease-inhibitors (ritonavir/lopinavir): co-administration of verapamil with ritonavir may result in elevated plasma concentrations of both drugs. Ritonavir can prolong the PR interval in some patients; however, the impact on the PR interval of coadministration of ritonavir with other drugs that prolong the PR interval (including calcium channel blockers) has not been evaluated. If coadministration of these drugs is warranted, do so with caution and careful monitoring. Decreased calcium-channel blocker doses may be warranted. Monitor PR interval.
* Beta-Blockers: co-administration of Beta-blockers and verapamil can lead to significant AV nodal blockade. This can manifest as heart block, bradycardia, cardiac conduction abnormalities and/or prolonged PR interval. Congestive heart failure or severe hypotension also can occur. The combination of beta-blockers and verapamil should be avoided in patients with poor ventricular function due to increased negative inotropic effects. Monitor heart rate and PR interval.
* Antihypertensive agents (eg, vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta-blockers): Verapamil administered concomitantly with oral antihypertensive agents can lead to an excessive reduction in blood pressure. Patients receiving these combinations should be appropriately monitored.

## **5.6. QT monitoring**

Drug-induced QT prolongation is regarded as a surrogate indicator for increased risk of drug-associated torsades de pointes (TdP), a potentially lethal polymorphic ventricular tachycardia. However, the relationship between QT prolongation and risk of TdP is imperfect and complex. The risk of TdP is not a linear function of QT duration nor the extent of change; some drugs which prolong QTc as amiodarone are not clearly associated with increased arrhythmic death(6)**.**

### 5.6.1 Management of QT prolongation. Recommendations.

**1)** The antimalarial drugs chloroquine and hydroxychloroquine are known to prolong QT. Their efficacy against COVID-19 remains to be validated in larger randomized studies. If there is concomitant administration of these drugs with amiodarone is advised closer ongoing monitoring, dose adjustment and drug discontinuation according to the following modified scheme from the American College of Cardiology
[7]:

1. Closer monitoring of QT length with telemetry or repeated ECGs daily.
2. Monitor and optimize serum potassium daily.
3. If QTc increases by >60 msec or absolute QTc >500msec (or >530-550 msec if QRS >120 msec), discontinue azithromycin (if used) and/or reduce dose of hydroxychloroquine and/or reduce dose of amiodarone and repeat ECG daily.
4. If QTc remains increased >60 msec and/or absolute QTc >500 msec (or >530-550 msec if QRS >120 msec), reevaluate the risk/benefit of ongoing therapy, and consider discontinuation of hydroxychloroquine.

**2)** It is important to monitor electrocardiogram, particularly QT intervals and treat electrolytes imbalances as hypokalemia and hypomagnesemia which can prolong QT.

To aid in the risk stratification for drug-associated QTc prolongation the following risk score can be used:

**Table 5. Risk Score For Drug-Associated QTc Prolongation**

|  |  |
| --- | --- |
| Risk Factors | Points |
| Age ≥68 y | 1 |
| Female sex | 1 |
| Loop diuretic | 1 |
| Serum K+ ≤3.5 mEq/L | 2 |
| Admission QTc ≥450 ms | 2 |
| Acute MI | 2 |
| ≥2 QTc-prolonging drugs | 3 |
| Sepsis | 3 |
| Heart failure | 3 |
| One QTc-prolonging drug | 3 |
| Maximum Risk Score | 21 |
| K+ indicates potassium; and MI, myocardial infarction. |

Risk Levels: a score of ≤ 6 predicts low risk, 7-10 medium risk, and ≥ 11 high risk of drug-associated QT prolongation.

# **6. Study Assessment and Procedures**

## **6. 1 General information**

Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Procedures conducted as part of the participant’s routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

## **6.2 Standard treatment of Coronavirus Disease 2019 (COVID-19)**

Usual care means: oxygen therapy for hypoxemia, symptomatic treatment for the comfort and well-being of the patient (e.g. rest, fluid therapy, pain relievers, antipyretics), anticoagulant prophylaxis and drugs with supposed or documented antiviral activity recommended in local guidelines.

## **6.3 Schedule of Activities (SoA)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Phase of study/ Point of time** | **Day 1 screening/ enrolment** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 6** | **Day 7** | **Day 8** | **Day 9** | **Day 10** | **Day****11** | **Day****12** | **Day 13** | **Day 14** | **Day 15**+/- 2 days | **Day 28 or discharge**+/- 2 days**(End of Study)** |
| Informed Consent | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| I/E Criteria | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Randomisation | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood / urine pregnancy test1 | X2 |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X |
| Medical History3 & Demographics4 | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| COVID-19 Symptoms5 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination6 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Score on 7-point ordinal scale7 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| NEWS2 score8 | X |  |  |  |  |  | X |  |  | X |  |  |  |  | X | X |
| Height and Weight, BMI | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Body Temperature9 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Blood pressure & Heart Rate10 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Respiratory rate | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Oxygen saturation (O2 sats)11 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Is oxygen therapy necessary? Kind of oxygen support | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

**Table 4. Schedule of Activities (SoA)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| The oxygenation index12 | X |  |  |  |  |  | X |  |  | X |  |  |  |  | X | X |
| 12-lead ECG with QT and QTc monitor13 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Serum potassium level14 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Serum sodium level | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serum calcium level (total calcium) | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serum creatinine | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| AST, ALT | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Troponin level15 | X |  |  |  |  |  | X |  |  | X |  |  |  |  | X |  |
| D-dimer15 | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Creatine kinase15 | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Creatine kinase-MB15 | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| C-reactive protein level | X |  |  |  |  |  | X |  |  | X |  |  |  |  | X | X |
| PLT, WBC, Lymphocytes | X |  |  |  |  |  | X |  |  | X |  |  |  |  | X | X |
| TSH, fT3 and fT4 | X16 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Echocardiogram15,17 | X |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X |
| IMP administration18 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X19 |
| Adverse event monitoring | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| RT-PCR SARS-CoV-220 | X |  |  |  |  |  | X15 |  |  |  |  |  |  |  | X | X15 |

**1** Applicable only for women of child-bearing potential

**2** The result of this pregnancy test must be available and negative before the first IMP can be taken.

3 Medical history: cardiovascular disease, diabetes, cancer, chronic obstructive pulmonary disease

4 Demographics: age and sex

5 COVID-19 Symptoms: fever, cough, dyspnoea, muscle or joint pain, diarrhea, fatigue, chest pain, headache.

6 Physical examinations will cover the following body systems: general appearance, skin, neck (including thyroid), throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, neurological systems, and, if applicable, others.

7 WHO classification, that was used in recent COVID-19 trials [8]:

The ordinal scale has the following items, ranging from 1 to 7:

1. Death.
2. Hospitalized patients who require mechanical ventilation, ECMO, or both;
3. Hospitalized patients who require nasal oxygen therapy in high flow, non-invasive mechanical ventilation, or both;
4. Hospitalized patients who require oxygen therapy;
5. Hospitalized patients who do not require oxygen therapy;
6. Not hospitalized, but unable to resume normal activities;
7. Not hospitalized with resumption of normal activities;

8 NEWS 2 (National Early Warning Score 2) including: respiratory rate (breaths per minute), oxygen saturations (%), any supplemental oxygen, body temperature, systolic blood pressure (mmHg), heart rate (BPM), level of consciousness.

9 Body temperature can be measured in the armpit or in the oral cavity (under the tongue) or in the rectum. Body temperature should be measure twice a day (at 8.00 a.m. and 8.00 p.m.) and as soon as possible after randomization in the same body part every day. Temperature should be measured by digital thermometer (the same thermometer every times) and at least 30 minutes after: exercising, bathing, eating or drinking. Fever is defined as body temperature ≥36.6°C [axilla], or ≥37.2 °C [oral], or ≥37.8°C [rectal].

10 Blood pressure (systolic and diastolic), and heart rate to be measured with the patient in a seated position, after at least 5 minutes at rest.

11 Oxygen saturation measured using non-invasive pulse oximetry device. A sensor should be placed on the forefinger or forehead. Oxygen saturation should be measured at least twice a day (at 8.00 a.m. and 8.00 p.m.) and as soon as possible after randomization. Oxygen saturation should be measured by the same device every times and in the same place.

12 PO2/FIO2 oxygenation index defined as quotient of partial pressure of oxygen in arterial blood (PaO2, in mmHg) and fraction of inspired oxygen (FiO2)

13 The 12-lead ECG (I, II, III, aVR, aVL, aVF, V1-V6) will be recorded in supine position after at least 5 minutes at rest using the local standard ECG machine. *The ECG will be analyzed qualitatively (normal or abnormal, if abnormal clinically significant [yes/no]). The hearth rhythm and hearth arrhythmias, heart rate, PQ-, QRS-, and QT-intervals, as well as the heart rate-corrected QTc interval (according to Bazett’s formula) will be determined*. All procedures will be done according to local practice.

14 It is necessary to measure serum potassium level on the first day of the study. The frequency of serum potassium level measurement in the following days is up to the co-invastigator to decide. Normokalemia should be maintained.

15 If possible. Test recommended but optional.

16 Only if they are clinical signs and symptoms of thyroid disease.

17 Ejection fraction (%) and pulmonary artery pressure (mmHg).

18 For detailed IMT administration see section 5. Administration of IMP: amiodarone or verapamil.

19 Only if there is cardiovascular indication to prolong IMP treatment.

20 Positive or negative test result. If available: mean viral load (log10 copies per ml)

# **7. Endpoints**

## **7.1. Primary endpoint**

The primary end point of the study is the **clinical improvement**  defined according to WHO classification, that was used in recent COVID-19 trials [8]. The end point is defined as time to first occurrence of clinical improvement assessed on a seven category scale ranging from 1 to 7. Improvement is considered as the increase of one category of the scale or discharge. Lower scores indicate worse outcomes and higher scores outcome improved.

The ordinal scale has the following items, ranging from 1 to 7:

1. Death.
2. Hospitalized patients who require mechanical ventilation, ECMO, or both;
3. Hospitalized patients who require nasal oxygen therapy in high flow, non-invasive mechanical ventilation, or both;
4. Hospitalized patients who require oxygen therapy;
5. Hospitalized patients who do not require oxygen therapy;
6. Not hospitalized, but unable to resume normal activities;
7. Not hospitalized with resumption of normal activities;

## **7.2. Secondary endpoints:**

* Mortality. [Time Frame: Randomization to day 28 or discharge].
* Clinical improvement at 28 days.
* Time to clinical improvement.
* Duration of hospitalization. [Time Frame: Randomization to day 28 or discharge].
* Days of oxygen therapy.
* Mechanical ventilation.
* Change in NEWS2 score. The National Early Warning Score (NEWS2) score. A higher score is worse. [Time Frame: Randomization to day 7 and 15]. Score ranges from 0-20.
* Clinical improvement or fever resolution. Composite endpoint. [Time Frame: Randomization to day 7, 15 and 28 or discharge].
* Tachyarrhythmias defined as atrial fibrillation, supraventricular or ventricular tachycardia requiring treatment. [Time Frame: Randomization to day 28 or discharge].
* Mortality or tachyarrhythmias. Composite endpoint. [Time Frame: Randomization to day 28 or discharge].
* Time to clinical improvement from admission using the 7-point ordinal scale. [Time Frame: Randomization to day 28 or discharge].
* PO2/FIO2 oxygenation index defined as quotient of partial pressure of oxygen in arterial blood (PaO2, in mmHg) and fraction of inspired oxygen (FiO2) [Time Frame: Randomization to day 7 and 15 and discharge].
* Time to resolution of fever [Time Frame: Baseline to Day 28 ] Defined as body temperature (≤36.6°C [axilla], or ≤37.2 °C [oral], or ≤37.8°C [rectal]) for at least 48 hours without antipyretics or until discharge, whichever is sooner. [Time Frame: Randomization to day 28 or discharge].

## **7.3 Biomarker and laboratory values assessment**

The following parameters will be assessed at baseline, 7, 10 and 15 days: C-Reactive

protein, high-sensitivity (hs) cardiac troponins, platelet count, D-dimers, white blood cells (WBC), lymphocytes, creatine kinase(CK)- myocardium brain(MB).

# **8. Randomization design**

The planned scheme is 1:1:1 randomization with permuted blocks (3 6 9), stratified by oxygen therapy (yes/no), to ensure balanced allocation between the randomized groups.

# **9. Statistical analysis plan**

The primary analysis will be based on the principle of intention-to-treat. The null hypothesis for this analysis is that the hazard ratio (HR) for the experimental groups of amiodarone or verapamil compared to current treatment (H0) = 1. The alternative hypothesis is that the HR for the experimental groups of amiodarone or verapamil (HA) ≠ 1. A test of superiority at the two-sided 0.05 level will be performed using a Cox proportional hazard model that includes treatment group as a covariate. A point estimate and two-sided 95% CI for the relative risk as measured by the HR will be calculated based on the Cox proportional hazards model.

Power calculations are based on a superiority comparison for the primary efficacy endpoint of clinical improvement in favor of amiodarone or verapamil vs current strategies alone. A two-sided logrank test with an overall sample size of 804 subjects (268 per arm) achieves 80% power at a 0,05 significance level when the proportion assuming clinical improvement in the control group to be 30% (8) and in the experimental group (amiodarone or verapamil) 39%, with a 2% dropout rate.

**Prespecified analyses**

Analyses be conducted to test the association between laboratory parameters (cfr **Section 7.3**) and mortality. Peak and nadir values will be tested and the levels serially assessed at 7, 10 and 15 days. Cluster analysis to identify distinct phenogroups will be performed.

Prespecified subgroup analyses include patients with cardiovascular disease, patients with early (≤7 days) vs later onset of symptoms, diabetes, gender.

**Event Adjudication**

Clinical events will be validated blindly by an independent clinical event committee (CEC) unaware of the treatment allocation.

# **10. Adverse Events and Serious adverse events reporting**

## **10.1. Definitions**

Adverse Events (AE) is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.

## NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment..

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

- Results in death

- Is life-threatening

- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent disability/incapacity

- Is a congenital anomaly/birth defect

 - Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction (SAR) that is unexpected or for which the development is uncommonly (unexpected issue) observed during a clinical trial and for which there is at least a reasonable possibility of a causal relationship with the IMP.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study.

Serious adverse events (SAEs) will be reported and evaluated by a safety committee who will oversee the study conduction.

* The means of obtaining AE data should be described (volunteered, checklist, or questioning) as should any specific rating scales used and any specifically planned follow-up procedures for specific AE or any planned rechallenge procedures in case study treatment is discontinued because of an AE.
* Consider whether there any protocol-specific events that may need expedited reporting, or alternatively, are not required to be reported. Provide guidance for investigators.
* If there is a specific AE that will be of particular interest it should be described in a sub- section (AE of Special Interest). The description should include the following:
	+ The definition of the event.
	+ Is it a measurable quantity? If yes, how will the measurement be done?
	+ If it is a clinical event, how will it be confirmed?

**NOTE: Level 3 headings** **in this section are common text and must be maintained in order to ensure the elements required by ICH and regulators are included in the protocol.**

## **10.2. Time Period and Frequency for Collecting AE and SAE Information**

All SAEs will be collected from the signing of the ICF until Day 28 (End of Study) at the time points specified in the SoA .

All AE will be collected from the signing of the ICF until Day 28 (End of Study) at the time points specified in the SoA.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

## **10.3. Method of Detecting AEs and SAEs**

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non‑leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

For some studies, participants are not always able to provide valid verbal responses to open‑ended questions. In these circumstances, another method of detecting AEs and SAEs must be specified.

## **10.4. Follow-up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

## **10.5. Regulatory Reporting Requirements for SAEs**

* Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
* The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Independent Ethics Committees (IEC), and investigators.
* Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
* An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator’s Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

# **11. Pregnancies**

Should a pregnancy occur in a female patient, or in a female partner of a male patient, it must be reported to the sponsor within 24 hours of the first awareness of the event. The trial participation of patients who become pregnant during the trial after signing the informed consent will be discontinued immediately.

# **12. Patient withdrawal from trial participation**

Participation in the trial is voluntary and patients may withdraw from the trial at any time and for any reason. However, all patients will be encouraged to complete the trial. All patients withdrawing from the trial will be encouraged to complete the EoS assessment 28 days (+/- 2 days) after the last intake of the IMP.

The primary reason leading to patient withdrawal will be documented as:

• Patient withdraws consent due to

o AE(s)

o other reason (to be specified)

• Investigator decision due to

o AE(s), which in the opinion of the investigator may jeopardize the patient’s health or may compromise the trial objectives

o relevant non-compliance with the protocol, which in the opinion of the investigator may jeopardize the trial integrity or scientific goals of the trial

o reasons other than AE or non-compliance (to be specified)

• Pregnancy

• Treatment with prohibited concomitant medication

• Violation of inclusion or exclusion criteria noted only after randomization

• The trial is terminated by the sponsor

The primary reason for discontinuation from the trial is to be recorded in the source documents and on the early termination page of the eCRF.

If the patient withdraws consent, no further evaluations should be performed and no attempts should be made to collect additional data.

Patients who prematurely discontinue the trial will be treated according to the investigator’s discretion and standard treatment guidelines, irrespective of the reason for withdrawal, and will not be replaced.

Reasonable efforts will be made to contact any patient lost to follow up, to complete assessments (including an EoS assessment) and to retrieve any outstanding data and IMP and supplies.

If the IMP will be prematurely discontinued, the primary reason for discontinuation is to be recorded in the appropriate section of the eCRF. Patients who discontinue therapy with IMP will be encouraged to continue with study-related assessments (including EoS visit) until their trial completion.

# **13. Lost to Follow Up**

Include a brief section on how the study will define and address lost to follow-up participants to help limit the amount and impact of missing data.

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

* The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
* Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient’s last known mailing address or local equivalent methods). These contact attempts should be documented in the patient’s medical record.
* Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

# **14. Ethical and legal requirements**

## **14.1. Ethical conduct of the trial**

The trial will be conducted in a manner consistent with all applicable regulatory authority and IEC regulations (e.g. International Council for Harmonisation [ICH] Guideline for Good Clinical Practice [GCP, CPMP/ICH/135/95] and the Declaration of Helsinki [version of 1996]) as well as in keeping with applicable local law(s) and regulation(s). The investigator must also comply with all applicable privacy regulations (for EU: General Data Protection Regulation).

## **14.2. Independent ethics committee**

Before the initiation of the clinical trial, the final protocol, any amendments if applicable, the patient information sheet and consent form, as well as any additional documents which are required by national regulations and the IEC will be submitted to the competent IEC for review. A favourable opinion for the clinical trial must be obtained from the IEC before any patient is enrolled at a site.

If appropriate, any additional requirements imposed by the IEC will be followed. Amendments to the trial documents will be notified to, or approved by, the IEC before implementation, if applicable.

## **14.3. Patient information and consent procedure**

Before any clinical trial-related activities are performed, the investigator (or authorized designee) must review the informed consent form and explain the trial to potential trial participants. The investigator must ensure that the patient is fully informed about the aims, procedures, potential risks, any discomforts, and expected benefits of the clinical trial. Before consenting, the patient must be left with ample time to consider and ask questions. It must be emphasized that participation is voluntary and that the patient has the right to withdraw from the clinical trial at any time without prejudice. The patient and the investigator must then sign and date the consent form before the conduct of any trial procedures.

A copy of the patient information and informed consent form will be given to the patients for their records. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this clinical trial.

If amendments to the final trial protocol affect the patient’s participation in the clinical trial (e.g. a change in any procedure), the patient information and informed consent form must be updated to incorporate this modification, and patients must agree to sign the amended form indicating that they re-consent to participate in the clinical trial.

## **14.4. Insurance coverage**

Insurance coverage for damages emerging from the clinical trial will be provided according to applicable legal requirements. During the informed consent procedure, the investigator must inform the patient accordingly. Insurance details will be provided to the patient within the patient information sheet.

## **14.5. Submission to authorities**

## Documents required for the trial application will be submitted to the responsible competent authority (CA). The trial will not start until this authority has authorized the trial. Amendments to the trial protocol or to any other documents that must be reviewed by the CA will also be submitted to the CA in accordance with the regulatory requirements. If applicable, approval of the amendment must be awaited before implementing any changes.

## **15. Patient confidentiality**

The trial protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the clinical trial or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Personal patient data will be kept confidential in compliance with the General Data Protection Regulation, and other applicable international and national requirements.

The investigator must ensure that the confidentiality and anonymity of trial participants will be maintained and that their identities are protected from unauthorized parties. In eCRFs, compensation documentation, or any other documents submitted to the sponsor or sponsor’s designee, patients must be identified only by their identification codes; it is not allowed to use their names, addresses, telephone numbers, or similar information. The investigator will keep the original of the Patient Identification Log (including complete name and date of birth of each patient) in his/her file. The investigator must maintain these documents in strict confidence.

To allow compliance with GCP, all patients will be asked for consent regarding the access to their personal clinical trial-related data for monitoring, audits, and inspections as well as regarding transmission and storage of their pseudonymous data; a respective statement will be part of the informed consent form. Professionals getting access to source

# **16. Data collection, monitoring and quality assurance**

## **16.1 Data collection**

All data will be collected on an eCRF separately for each patient. eCRFs will be provided as a regulatory compliant, electronically secure and protected web-based database, and will be handled in accordance with the instructions provided. An audit trail will record all entries and corresponding changes.

The trial sites will be provided with secure access to and training on the eCRF.

All data generated after the patient provided informed consent must be recorded in the eCRF. The treating investigator is responsible for ensuring accurate and proper completion of the eCRF.

Only treating physician and authorized designees will enter and edit data via a secure network and a secure access system. Completed data for each visit will be approved by the investigator or authorized designee using an electronic signature to confirm the accuracy of the data. Any change or addition will be recorded by an electronic audit trail system.

The investigator or designee has to carefully answer queries issued by data management.

## **16.2 Source data**

Source data are defined as all data in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial (see ICH E3 GCP, 1.51). Source records should be stored for a time period as defined by local regulations.

The investigator must keep a patient file (medical file, original medical records) on paper or electronically for every patient included in the trial.

It must be possible to identify each patient by using this patient file. Dates and authors of all source data entry and changes must be clearly identifiable.

Documents and data to be considered source data will be identified and agreed with the investigator in advance of the first screening visit. The location of all source data will be documented and filed in the Investigator Site File (source data location form). Electronic patient files will be printed whenever the monitor performs source data verification. Printouts must be signed and dated by the investigator, countersigned by the monitor, and filled at the center as required for other source data documents.

## **16.3 Monitoring**

The extent and details of monitoring including source data verification will be specified in the monitoring plan.

During the trial, further monitoring visits will be performed according to ICH GCP, the sponsor’s designee’s or local CRO’s standard operating procedures, and local regulations. eCRFs will be reviewed against source data for adherence to the trial protocol and ICH GCP, as well as for completeness, accuracy, and consistency of data. Additionally, the monitor will check the progress of enrolment, and will ensure that the IMP is being stored, dispensed and accounted for according to specifications. Key trial personnel must be available to assist the monitor during these visits.

The investigators must permit the monitor`s access to the patient’s medical records and all applicable source documents. Throughout the trial, all data captured in the eCRF will only be identified by patient number. The data will be blinded correspondingly in all data analyses.

It is the investigators’ obligation to assure documentation of all relevant data in the patient’s file, such as medical history and concomitant diseases, date of trial enrolment, visit dates, results of examinations, administrations of IMP and any concomitant medication, and AEs.

## **16.4 Audits and inspections**

During the trial, audits may be performed by independent auditors. Audits of clinical research activities will be performed in accordance with corresponding standard operating procedures to ensure compliance with the principles of GCP.

Regulatory authorities may wish to conduct an inspection. If an inspection is requested, the investigator must inform the sponsor or sponsor’s designee immediately.

The investigator must allow auditors or inspectors access to source data and documents and will answer any questions.

## **16.5 Data management procedures**

All data management activities will be conducted by the sponsor’s designee following their standard operating procedures. Details on data handling will be described in the data management plan. Data entered into the eCRF will be validated through online edit checks and offline checks run by the data manager according to the data validation plan. For all identified discrepancies, the data manager will raise a query in the electronic data capture application. The appropriate investigational personnel will answer the queries in the eCRF, which will be audit trailed by the electronic data capture application.

The sponsor’s designee will handle the data cleaning process, query process, and coding.

For the main analysis, the respective database will be locked when it is considered complete and accurate and after all changes following the data review meeting (if applicable) are included (i.e. all data cleaning activities performed). All changes will be tracked (audit trail). Sponsor approval prior to database lock is mandatory.

## **16.6 Trial report and publications**

The results of the main treatment period will be summarized in a clinical trial report according to the ICH E3 Note for guidance on structure and content of clinical trial reports. Results of the extended treatment period will be reported in an addendum to the clinical trial report.

Regular safety update reports will be submitted to investigators as well as to regulatory authorities and IECs, as appropriate, within the timeframes defined per national regulation or by the IEC.

The preparation and submission of abstracts or manuscripts including the trial results will be coordinated by the steering committee. The publication or presentation of any trial results shall comply with all applicable privacy laws.

# **17. Trial periods**

Estimated start: May 2020 (first patient in)

Estimated end of treatment: December 2020 (last patient EoS visit)

Estimated recruitment period: 8 months

The end of the trial is defined as last patient visit, i.e. the EoS visit, in any participating site.

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