Parexel International

ABIVAX

ABX464-401

A phase 2/3, randomized, double blind, placebo-controlled study to evaluate the efficacy and the safety of ABX464 in treating inflammation and preventing COVID-19 associated acute respiratory failure in patients aged ≥ 65 and patients aged ≥ 18 with at least one additional risk factor who are infected with SARS-CoV-2. (the MiR-AGE study).

Statistical Analysis Plan

Version: 5.0

Parexel Project Number: 252421

SPONSOR SIGNATURE PAGE

Signature below indicates that you have reviewed the document for clarity, completeness and consistency and approve it.

This document has been approved and signed electronically by the following:

Signature:		
Print Name:	Paul Gineste	Title: Vice President of Clinical Operations

Parexel SIGNATURE PAGE

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	11 Sep 2020	New document
2.0	19 Jan 2021	Changed interim analyses from superiority/futility to futility only and changed the futility boundary. Changed the rules for sample size re-estimation at the interim analysis and consequently the final analysis of the primary efficacy endpoint. Clarity on derivation of primary endpoint added; SpO2 measured by a medically trained person will be used only (diary data are excluded). Completed Appendix 6.2 Prohibited Medications with WHO Drug Dictionary codes. Typo corrections.
3.0	01 Mar 2021	Review History date for version 2.0 corrected from dd Mmm 2021 to 19 Jan 2021. Primary endpoint outcome labels were amended for clarity: NO to NON-RESPONSE, YES to RESPONSE. Contributing endpoint were amended alike. Oxygen supplementation (a): OCCURRED to YES, NO to YES; Mechanical ventilation (b): YES to NO, NO to YES; Death (c) DIES to YES, ALIVE to NO. In accordance with these changes Table 4 was changed also. Changes did not affect the underlying logic only the outcome labels were changed.

4.0	07 May 2021	Upon sponsor decision all efficacy related analyses are removed, only safety related analyses are left in the SAP supporting abbreviated reporting.
5.0	16 Jun 2021	Added version history item for Version 4.0. Added derivation logic for flagging adverse event leading to study discontinuation flag in AE section 4.11.1.

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
ACE2	Angiotensin converting enzyme 2
ADI	Actual Dose Intensity
AE	Adverse event
ARDS	Acute Respiratory Distress Syndrome
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CMDC	Carbon Monoxide Diffusing Capacity
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRP	C-reactive Protein
CS	Clinically Significant
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
CV	Coefficient of Variation
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DRM	Data Review Meeting
DSMB	Data and Safety Monitoring Board
ECMO	Extracorporeal Membrane Oxygenation
EOS	End-of-study
EOT	End-of-treatment
ET	Early Termination

Abbreviation / Acronym	Definition / Expansion
FAS	Full Analysis Set
FEV	Forced Expiratory Volume
ICF	Informed Consent Form
IL	Interleukin
IMP	Investigational Medicinal Product
IMV	Invasive Mechanical Ventilation
INF	Interferon-gamma
MAR	Missing at Random
MCAR	Missing Completely at Random
MCP	Monocyte Chemoattractant Protein
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing Not at Random
MRC	Medical Research Council
MV	Mechanical Ventilation
NA	Not Available
NCS	Not Clinically Significant
NIV	Non-invasive Mechanical Ventilation
NK	Not Known
O2SUP	Oxygen Supplementation
PBMC	Peripheral Blood Mononuclear Cell
PDI	Planned Dose Intensity
PFT	Pulmonary Function Tests
PP	Per Protocol Set
PT	Preferred Term
QD	Once a Day
RDI	Relative Dose Intensity
RFDP	Respiratory Failure or Death Prevented

Abbreviation / Acronym	Definition / Expansion
RNA	Ribonucleic Acid
rtPCR	Real-time PCR
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SARS	Severe Acute Respiratory Syndrome
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SOC	System Organ Class
SpO2	Oxygen Saturation
STAT	Signal Transducers and Activators of Transcription
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Event
TLFs	Tables, Listings, and Figures
TNF	Tumor Necrosis Factor
TTH	Time to Hospitalization
TTMV	Time to Mechanical Ventilation
TTO2	Time to Oxygen Supplementation
VC	Vital Capacity
WHO-DD	World Health Organization - Drug Dictionary

1 INTRODUCTION

A novel coronavirus SARS-CoV-2 (previously known as 2019-nCoV) was identified in 2019 in Wuhan, China. This is a new coronavirus that has not been previously identified in humans. The precise etiology is unknown and therefore medical therapy to cure the disease is not yet available.

The coronavirus disease 2019 (COVID-19) is an acute respiratory disease caused by this novel coronavirus, that shows sustained human-to-human transmission, and has been exported around the globe to reach pandemic proportion. The novel coronavirus uses the same cell surface receptor, angiotensin converting enzyme 2 (ACE2) as SARS-CoV, for entry, and infects preferentially the respiratory tract where this receptor is expressed. The elderly and people with underlying diseases are most prone to serious outcomes, which appear to be associated with acute respiratory distress syndrome (ARDS) and cytokine storm syndrome.

ABX464 is a novel, oral, safe and potent anti-inflammatory drug candidate, with impressive Phase 2a clinical results in ulcerative colitis. ABX464 selectively up-regulates a microRNA, mir-124, a physiological negative regulator of inflammation, that acts on several key pathways of inflammatory cytokines signaling, especially STAT3 (Signal Transducers and Activators of Transcription).

ABX464 has the potential to alter the clinical course of Covid-19 infection by limiting the body's cytokine-mediated inflammatory response (cytokine storm).

As part of data and safety monitoring per protocol, a data and safety monitoring board (DSMB) meeting held on 04 March 2021 concluded to study futility and recommended study termination. The Sponsor accepted this recommendation to terminate the study. Consequently, efficacy results and related analyses will no longer be in the scope of this Statistical Analysis Plan (SAP). Details on analyses removed from the scope of SAP is provided in Section 4.13, in Changes in the Conduct of the Study or Planned Analysis.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 4.0 (Nov 12, 2021)
- Electronic Case Report Form (eCRF), Version 4.1 (Nov 18, 2020)

2 STUDY OBJECTIVES

2.1 Primary Objective

With reference to Section 4.13, the primary objective is removed the scope of this SAP.

2.2 Secondary Objectives

Per protocol secondary objectives, other than evaluation safety from D0 to D48, are removed from the scope of this SAP (refer to Section 4.13).

2.3 Exploratory Objective

With reference to Section 4.13, the exploratory objectives are removed the scope of this SAP.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

ABX464-401 is a phase 2/3 study evaluating the efficacy and safety of ABX464 50mg once daily (QD) (oral capsule), on treating inflammation and preventing acute respiratory failure in patients infected with SARS-CoV-2.

Eligible patients will be randomized according to a 2:1 ratio into 2 treatment cohorts as follows:

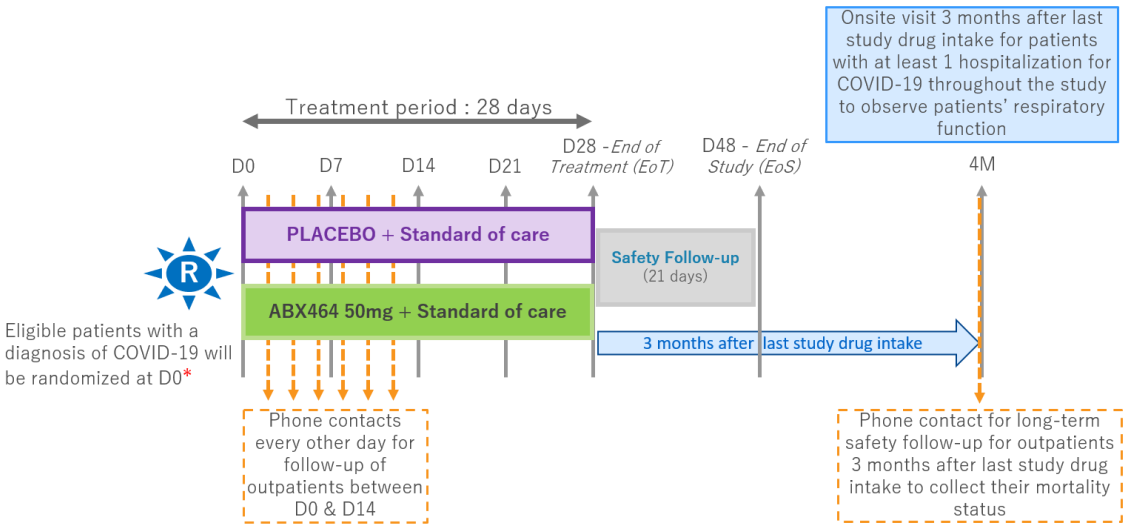
- Standard of Care (SoC) + ABX464 50mg QD cohort: 533 patients
- Standard of Care + Placebo QD cohort: 267 patients

Upon randomization, patients will be stratified according to:

- Age ⩾ 65 years or < 65 years (with at least one risk factor)
- Inpatient or outpatient, at the time of enrolment

The study will consist of 3 periods:

- Treatment phase: randomized patients will be treated for 28 days
- Safety follow-up phase of 21 days
- Exploratory follow-up of the pulmonary function 3 months after the last study drug intake.



** Considering sites potential organization and the quarantine requirements in participating countries, randomization visit can be splitted into 2 separated visits. However, the interval between these 2 visits cannot exceed 48 hours to ensure patients start the study treatment at an early stage of the disease.*

From Day 0 onwards, randomized patients will be followed by the investigational site at 7 days (D7 +/- 2 days), 14 days (D14 +/- 2 days), 21 days (D21+/- 2 days), 28 days (D28 +/- 2 days) and finally at 48 days (D48 +/- 2 days), after randomization.

A long-term follow-up is scheduled as an onsite visit for patients having been hospitalized during the course of the study. This follow-up will be performed 3 months after the last study drug intake and will consist of a respiratory function exploration. In addition, investigators will report the disease severity rating using a 7-point ordinal scale.

An independent DSMB, with expertise and experience in virology and immunology, and without direct involvement in the conduct of the trial, will be set up specifically to guarantee effective protection of patients, ensure the ethical conduct of the trial, benefit/risk ratio of the trial, and to ensure the independent review of the scientific results during the trial and at the end of the trial. The DSMB will meet first after the 20 first patients are enrolled and treated for at least 4 weeks (D28) and then every month after this first meeting.

A study steering committee will oversight the practical aspects of the study especially with regards to the evolving nature of the COVID-19 infection. The Steering Committee will work in conjunction with the DSMB. The Steering Committee will be able to terminate the trial if the medical relevance of the MiR-Age is substantially modified during its execution. ABIVAX and principal investigator will agree, in writing prior to the start of the study, to the charter of the Steering Committee.

One interim analysis is planned after approximately 300 of randomized patients' complete day 28 assessment or long term follow up period. Interim analysis will be performed without unblinding the sponsor as part of DSMB activities. The purposes for the interim analysis are to:

- assess the safety of the study treatment,
- potentially stop the study early due to efficacy/futility, or
- adjust the sample size.

3.2 Endpoints

3.2.1 Primary Efficacy Endpoint

Not applicable(refer to Section 4.13).

3.2.2 Secondary Efficacy Endpoints

Not applicable(refer to Section 4.13).

3.2.3 Safety Endpoints

- Physical examinations
- Vital signs (supine blood pressure [BP] and pulse, oral body temperature, SpO2)
- 12-lead electrocardiograms (ECG): Investigator interpretation
- Clinical laboratory tests (hematology and chemistry)
- Adverse event (AE) assessments
- Concomitant medication assessments

3.2.4 Exploratory Endpoints

Not applicable(refer to Section 4.13).

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

The overall outline of the scheduled assessment and other study procedures can be found in Table 3 Schedule of Assessments. In the following, the data handling conventions should be interpreted within the framework of the Schedule of Assessment.

4.2.1 Study Days

The date of Visit 1 is defined as Day 1. All other study days will be labeled relative to Day 1.

For observation/event dates on or after Day 1, study day for an observation/event date is derived as:

- Observation/event date – Visit 1 date + 1 day, which could be Day 1, Day 2, Day 3, etc.

For observation/event dates prior to Day 1, study day for an event date is derived as:

- Observation/event date – First infusion date, which could be Day -1, Day -2, etc., referring to 1 day, 2 days, etc., prior to Day 1, respectively.

Subsequently, Day 0 is not defined.

4.2.2 Definition of Baseline and Post-baseline Assessments

Baseline (derived) is defined as the last available assessment (scheduled or unscheduled) on Day 1. Assessments performed after Day 1 are considered post-baseline assessments.

Change from Baseline is derived where both baseline and post-baseline values are available:

- Change from Baseline = post-baseline value – Baseline value

End of Treatment (EoT) assessment is defined as the last available assessment (scheduled or unscheduled) assigned to treatment period.

End of Study (EoS) assessment is defined as the last available assessment (scheduled or unscheduled).

4.2.3 Analysis Periods, Visit Windows and Naming

Analysis periods will be derived for the statistical analyses based on the assigned analysis visits. Timing of analysis periods with start and end visits are tabulated in Table 1.

Table 1 Analysis Periods

Analysis Period	Start	End
Treatment Period	Visit 1 (Day 1)	Visit 5
Safety Follow-up Period	Visit 5 + 1 day	Visit 6
Long-term FUP	Visit 6 + 1 day	Visit 7
Overall Study Period	Visit 1 (Day 1)	Visit 7

As patients will not necessarily have their examinations at the exact scheduled visit time, it could be misleading if all data with the same nominal visit number are lumped together for a by-visit analysis. Thus, all post-baseline data (including both scheduled and unscheduled visits) will be “realigned” in the statistical analysis according to the appropriate window schema and according to the following general conventions.

The reference start day of the first visit window in the Treatment Period is Day 1. The start day of all other visit windows up to Visit 5 (Day 28) is the midpoint between the scheduled visit day for the previous visit ($Visit_{(i)}$) and the subsequent visit ($Visit_{(i+1)}$) plus 1 day: $(Visit_{(i)} + Visit_{(i+1)})/2 + 1$.

The end day of a visit window in the Treatment Period is the day prior to the start day of the next visit window with the exception of the last visit window, where the end day of the visit window will be the day of the EoT visit.

Safety Follow-up Period: Visit 6 (EoS) and Visit 7 (Long term FUP) assessments will be realigned utilizing the same general conventions but with the reference start day of the safety follow-up period derived relative to the last available assessment (scheduled or unscheduled) assigned to Treatment Period + 1 day (see Table 2).

Width of a realigned visit window will depend on the schedule of assessments for the respective type of assessment. That is, $Visit_{(i)}$ and $Visit_{(i+1)}$ day above refer to the visits as scheduled for the respective assessment and unless otherwise specified will be realigned per Table 2 (General realignment of visits).

Multiple assessments within visit windows

For visit windows multiple records may exist in one particular visit window for a particular assessment (i.e. laboratory assessments). The assessment closest to the actual target visit day is chosen as the analyzable record for both continuous variables and categorical variables. If two assessments have the same distance, then the earlier one by relative study day will be chosen as the analyzable record.

Early discontinuation visit remapping

Patients who prematurely discontinue from the study for any reason, will be scheduled for a Safety follow-up visit approximately 21 days following their last study drug intake, at which time all of the assessments listed for that visit will be performed. This visit will be assigned to Visit 6 (EoS).

Table 2 Visit Windows

Study Period	Visit Name	Target Visit Day	Start Day of Visit Window	End Day of Visit Window
Treatment	Visit 1	Day 1	1	1

Study Period	Visit Name	Target Visit Day	Start Day of Visit Window	End Day of Visit Window
	Baseline	Defined as the last available assessment (scheduled or unscheduled) on Day 1		
	Visit 2	Day 7	2	10
	Visit 3	Day 14	11	18
	Visit 4	Day 21	19	25
	Visit 5 (EoT)	Day 28	26	Date of study drug return.
	End of Treatment	End of Treatment is defined as the last available assessment (scheduled or unscheduled) assigned to Treatment Period.		
Safety Follow-up	Visit 6	Day 48	Date of study drug return + 1 day	Target visit day + 30 days
	Visit 7 (Long-term FUP)	Date of study drug return + 90 day	Target visit day - 10 days	Target visit day + 30 days
	End of Study	End of Study is defined as the last available assessment (scheduled or unscheduled) assigned to the Overall Study Period.		

4.2.4 **Analysis Conventions**

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in

the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

4.3 Handling of Dropouts or Missing Data

4.3.1 Imputation of Missing and Incomplete Dates/Times

Every effort will be made to collect complete dates for all study assessments. The following date imputation rules will be applied for missing or partial dates:

- If month and year available, set start date to latest of (1st of the month, first dose date), if end date is complete and imputed start date > end date, set imputed start date to end date – 1
- If year available: Set start date to latest of (January 1st, first dose date), if end date is complete and imputed start date > end date, set imputed start date to end date – 1
- If start date is completely missing, set to first dose date, if end date is complete and imputed start date > end date, set imputed start date to end date – 1.

Completely missing time information will be imputed as 00:00. Partially missing time information with missing hour (xx:mm) or minute (hh:mm) part will be imputed as 00:mm or hh:00, respectively. Missing part will be shown as NK in the listings (where NK = Not Known).

If time is not collected and date of assessment is the same as the first dose date, then assessment will be assumed to be collected prior to treatment unless schedule of assessments and protocol indicate planned collection is always after dosing.

Any AEs with incomplete start and end dates/times will be treated as follows:

Adverse events with unknown start and/or end times (but where the date is known) will be imputed with a time of 00:00 h for the tabulations but will be shown as NK: NK in the listings (where NK = Not Known).

Adverse events with completely unknown start dates will be considered as treatment-emergent for the tabulations and will be shown as NK in the listings. Partially complete AE dates will not be imputed in the listings and the available day, month and year components will be used to determine if an adverse event is treatment-emergent taking the first dosing date and end of study date as references.

Imputing partial AE and prior/concomitant medication start dates:

a) If the year is unknown, the date will not be imputed and will be assigned a missing value.

b) If the month is unknown, then:

   1. If the year matches the first dose date, then impute to the month and day of the first dose date.

   2. Otherwise, assign 'January'.

c) If the day is unknown, then:

   1. If the month and year match the first dose date, then impute to the day of the first dose date.

   2. Otherwise, assign '01'.

Imputing partial AE and prior/concomitant medication stop dates:

a) If the year is unknown, the date will not be imputed and will be assigned a missing value.

b) If the month is unknown, then assign 'December'.

c) If the day is unknown, then impute to the last day of the month.

4.4 Software

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment.

4.5 Study Patients

4.5.1 Disposition of Patients

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion.

Disposition summaries will be provided by treatment and overall. Number and percentage of patients with ICF, randomized and treated with any amount of study drug will be provided by country and overall). Number and percentage of patients who entered, completed and discontinued (with reason for discontinuation) a study period will be provided separately for treatment and follow up period.

Summary will include:

- the number of subjects randomized
- the number and percentage of subjects treated with any amount of study drug
- the number and percentage of subjects entering, withdrawing from study treatment, withdrawing from the study and completing each phase of the study by treatment group and overall. Withdrawals from the study and from study treatment will also be summarized by major reason.

By-patient listings of eligibility and randomization details, visit dates, and withdrawal details (including reason for discontinuation and duration of treatment prior to discontinuation) will also be provided.

4.5.2 Protocol Deviations

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived primary efficacy and/or safety of study treatments. The impact of major protocol deviations on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by major protocol deviations.

Major protocol deviations and any action to be taken regarding the exclusion of patients or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

Patients with less than 5 continuous days of IP treatment will be considered as a Major Protocol Deviation.

A summary of the number and percentage of patients with a major protocol deviation by treatment will be provided for each country and overall.

By-patient listing of major protocol deviations will be provided.

4.6 Analysis Sets

The following analysis sets will be defined and used for the analyses:

- Enrolled Analysis Set: all patients enrolled in the study. There will be no safety or efficacy analysis performed on this set.
- Safety Analysis Set: all patients randomized in the study to whom study medication has been dispensed. The safety analysis will be based on the actual study treatment dispensed.
- The Full Analysis Set (FAS): all patients randomized. Study treatment groups are defined by the randomized study treatment rather than the actual study treatment dispensed.

Upon database release, protocol deviation and analysis set outputs will be produced and will be sent to ABIVAX for review. An analysis set classification meeting will be arranged to discuss the outputs and to decide which patients and/or patient data will be excluded from certain analyses. Decisions made regarding the exclusion of patients and/or patient data from analyses will be made prior to unblinding and will be documented and approved by ABIVAX.

A summary of the number and percentage of patients assigned to analysis sets will be provided by treatment group and overall, for all enrolled patient.

A by-patient listing of analysis population details will be provided. This listing will be presented by treatment group and will include center, patient identifier, inclusion/exclusion flag for each population, and reason for exclusion from each population.

4.7 Demographic and Other Baseline Characteristics

Descriptive statistics (see Section 4.2) for demographics and other baseline characteristics and disease/medical history will be presented for patients assigned to FAS. All descriptive summaries will be presented overall and by country for each treatment group. Unless otherwise specified, percentages (%) will be based on the number of patients assigned to FAS (within subgroup stratification level, where relevant) with data available.

Original measurements, recorded in non-SI units will be converted to SI units for summaries as indicated below and will be listed in original and SI units:

$kg = lb \times 2.204$

$cm = in \times 2.54$

Demographics will be summarized, including:

- Age (years)
- Derived age category (< 65, ≥ 65 years)
- Sex
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other/Specification)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Stated, Unknown)
- Other Baseline characteristics, as recorded in the Vital Signs - Height and Weight eCRF at Visit 1
    - Height (cm).
    - Weight (kg).
    - Body mass index (BMI) (kg/m^2).

Baseline disease characteristics will be summarized, including:

- SARS-CoV-2 Status
- Days since onset of symptoms
- Risk factors associated to SARS-CoV-2 infection:
    - Age ≥ 65 years
    - Obesity defined as BMI ≥ 30 kg/m^2
    - Recent history of uncontrolled High Blood Pressure

- Treated diabetes (type I or II)
- History of ischemic cardiovascular disease

- Number of concurrent risk factors
- SpO2 (Visit 1)
- WHO Ordinal Scale (Visit 1)

Medical history/current medical conditions will be presented by treatment group and overall by number (n) and percentage (%) of all patients assigned to FAS according to the Medical Dictionary for Regulatory Activities (MedDRA version 23.0 or higher) primary system organ class (SOC) and preferred term (PT), regardless of whether the status is reported as ongoing or not ongoing at Visit 1. Unless otherwise specified, SOCs will be sorted alphabetically and within each primary SOC, the PTs will be sorted by descending order of total frequency (across all treatment groups combined). In the event of PTs with equal total frequencies, the relevant PTs will be sorted alphabetically. The number (n) and percentage (%) of patients having at least one medical history/current medical condition and having at least one medical history/current medical condition in each primary SOC, and for each PT will be presented. Hence if a patient reported more than one medical history/current medical condition with the same PT, the medical history/current medical condition will be counted only once. Similarly, if a patient reported more than one medical history/current medical condition within the same primary SOC, the patient will be counted only once at the SOC level.

Medical history/current medical condition, start date of event and ongoing status (yes/no) of each medical history/current medical condition as pre-specified in the Medical history eCRF will be presented in the by-patient data listing.

4.8 Prior and Concomitant Medication

Prior and concomitant medications will be analysed using the SAF. Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) Version March 2020 or later and will be classified by Anatomical Therapeutic Chemical (ATC) categories.

Prior and concomitant medications will be summarized separately. The number (n) and percentage (%) of patients taking medications will be summarized by ATC classification and PT, by treatment group and overall. Medications will be presented alphabetically by anatomical main group (the 1st

level of the ATC code). Within each ATC Level 1, the PTs will be sorted by descending frequency of the total number of patients with at least one medication in each PT. In the event of PTs with equal total frequencies, the relevant PTs will be sorted alphabetically. The number (n) and percentage (%) of patients having at least one concomitant or post-treatment medication in each ATC Level 1 and PT will be presented. Hence if a patient reported more than one concomitant or post-treatment medication with the same PT, the concomitant or post-treatment medication will be counted only once. Similarly, if a patient reported more than one concomitant or post-treatment medication within the same primary ATC Level 1, the patient will be counted only once. The overall number (n) and percentage (%) of patients receiving at least one medication and receiving at least one medication in each level of summarization will be presented relative to the total number of patients in the SAF.

Prior and concomitant medications (ATC Level 1/PT/Name), dose, frequency and route, start/stop date as specified in the Prior and Concomitant Medication eCRF with medication category (Prior only, both Prior and Concomitant or Concomitant only) will be presented in the by-patient data listing for FAS. Prohibited medications (Appendix 6.1) will be flagged in listings, as appropriate.

Medications will be categorized as follows:

Medication start and stop dates will be compared to the date of first dose of study medication to allow medications to be classified as either Prior or Concomitant. Medications starting after the treatment completion/withdrawal date will be listed but will not be classified or summarized.

Medications that start and stop prior to the date of first dose of study medication will be classified as Prior. If a medication starts before the date of first dose of study medication and stops on or after the date of first dose of study medication, then the medication will be classified as Concomitant. Medications will be classified as Concomitant if they have a start date on or after the date of first dose of study medication.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of study medication. If there is clear evidence to suggest that the medication started prior to the first dose of study medication, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped

prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be Prior only.

4.9 Treatment Compliance

Descriptive statistics for treatment compliance will be presented for patients assigned to SAF. Descriptive summaries will be presented for each treatment group and overall. Summary statistics will be provided for the following derived variables from data recorded in Drug Accountability eCRF:

$$Exposure\ duration\ (days) = \min(Date\ Returned, Date\ of\ Death) - Date\ Dispensed + 1$$

$$Compliance\ (\%) = 100 \times \frac{(Number\ of\ Tablets\ Dispensed - Number\ of\ Tablets\ Returned)}{Exposure\ duration}$$

By-patient listing of drug accountability data as recorded on eCRF with derived compliance data will be provided for SAF.

4.10 Efficacy Evaluation

Not applicable(refer to Section 4.13).

4.11 Safety Evaluation

All safety summaries and analyses will be based upon the Safety Set as defined in Section 4.6.

By-patient listings will include patient identifier, age, gender and race and will be sorted by patient, safety parameter and visit (if applicable).

4.11.1 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 and the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

An AE is any untoward medical occurrence in a study patient administered an IMP which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or

disease temporally associated with the use of an IMP, whether or not considered related to the IMP. Adverse events may include the onset of new illness and the exacerbation of pre-existing conditions.

Other untoward events occurring in the framework of a clinical study will be recorded as AEs, e.g. those occurring during treatment-free periods (including post-treatment Follow-up period), in association with study-related procedures and assessments.

Concomitant illnesses, which existed before entry into the clinical study, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded as part of the patient's medical history.

A treatment-emergent adverse event (TEAE) is defined as an AE that begins or that worsens in severity after at least one dose of the study drug has been administered.

Adverse event leading to study discontinuation is defined as an AE ongoing on the date of study discontinuation. Ongoing is defined as an AE started on or before and ended on or after the date of study discontinuation.

Summaries with number and percentage of patients reporting at least one adverse event and the total number of events will be reported by group and overall. Adverse event summaries will be provided separately for adverse events which occur or worsen from first dosing to Day 28 and adverse events which occur or worsen after Day 28.

- An overview on the number and percentage of patients with:
  - Any AE
  - Any AE of Grade 3 or higher
  - Any TEAE
  - Any TEAE of Grade 3 or higher
  - Any serious AE (SAE)
  - Any serious adverse drug reaction (SARs)
  - Any suspected unexpected serious adverse reaction (SUSARs)
  - Any treatment-emergent SAE
  - AE leading to death
  - TEAE leading to death
  - TEAE leading to treatment withdrawal
  - Any AE leading to study discontinuation

- TEAE leading to study discontinuation

- Number and percentage of patients for each TEAE, categorized by system organ class (SOC) and preferred term (PT)
- Number and percentage of patients for each TEAE of grade 3 or higher, categorized by SOC and PT
- Number and percentage of patients for each TEAE occurring in ≥ 5% of subjects in any treatment group, categorized by SOC and PT
- Number and percentage of patients for each TEAE, categorized by SOC, PT, and maximum CTCAE grade
- Number and percentage of patients for each TEAE, categorized by SOC, PT, and relationship to study drug
- Number and percentage of patients for each TEAE of grade 3 or higher, categorized by SOC, PT, and relationship to study drug
- Number and percentage of patients for each treatment-emergent SAE, categorized by SOC, PT, and relationship to study drug

Adverse event summaries will be ordered in terms of decreasing frequency for SOC and PT within SOC in the Total group and then alphabetically for SOC and PT within SOC. Summaries will be ordered in terms of decreasing frequency for PT in the Total group in summaries where SOC is not included.

For each patient and each adverse event, the worst severity (highest CTCAE grade) recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries. If CTCAE grade or causality is missing, a conservative approach for AE assessment (taking into account the worst case) will be followed.

A by-patient listing of all adverse events (including non-treatment-emergent events) will be provided. This listing will be presented by dose and will include patient identifier, age, sex, race, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, duration, severity, seriousness, outcome action taken (concerning both action with study drug and primary action (not related to study treatment)) and causality (concerning both study treatment and non-study treatment).

4.11.2 **Deaths, Serious Adverse Events, and Other Significant Adverse Events**

Other significant adverse events are those adverse events reported as leading to an intervention e.g. withdrawal from study, discontinuation of study treatment, introduction of concomitant medication, dose reduction. Following the specification provided for adverse AE summaries at section 4.11.1 summaries detailed below will be provided for deaths, SAEs and other significant AEs:

- Number and percentage of patients for each TEAE leading to death, categorized by SOC and PT
- Number and percentage of patients for each treatment-emergent SAE, categorized by SOC and PT
- Number and percentage of patients for each TEAE leading to study discontinuation, categorized by SOC and PT
- Number and percentage of patients for each TEAE leading to treatment withdrawal, categorized by SOC and PT

For deaths, SAEs and other significant AEs the following listings will be provided:

- A by -patient listing of all deaths that occurred during the study
- A by-patient listing of all serious treatment-emergent adverse events
- A by-patient listing of all TEAE leading to treatment withdrawal
- A by-patient listing of all TEAE leading to study discontinuation

4.11.3 **Clinical Laboratory Evaluation**

Laboratory values (hematology and biochemistry) will be summarized for all visits scheduled in treatment and follow up periods. Unscheduled visits will be listed only, unless contribute to baseline measurement.

The baseline for the laboratory values is defined as the last evaluable measurement before first dose, including any unscheduled assessment.

The Investigator will assess whether the values outside the clinical reference range are clinically significant and these will be reported as abnormal not clinically significant (NCS) or abnormal clinically significant (CS). Clinically significant laboratory values will be recorded by the Investigator as AEs.

Clinical laboratory parameters will be split into hematology and chemistry categories. The following summaries will be provided for all parameters:

- A summary of results by treatment group and visit.
- A summary of the change from baseline by treatment group and visit.
- Shift tables by treatment group and visit will be provided for all parameters to compare a patient's baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high.

By-patient listing will be provided for all patient enrolled by visit, including changes from baseline and reference range. All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings.

4.11.4 **Vital Signs, Physical Findings and Other Observations Related to Safety**

Vitals signs, ECG recording will be summarized for all visits scheduled in treatment and follow up periods. Unscheduled visits will be listed only, unless they contribute to baseline measurement.

Baseline is defined as the last evaluable measurement before first dose, including any unscheduled assessment.

Vital Signs

Following vital signs will be measured:

- Systolic blood pressure [mmHg]
- Diastolic blood pressure [mmHg]
- Pulse rate [beats/min]
- Body temperature (oral, tympanic or rectal) [°C or °F]
- Oxygen Saturation [%]

Investigators will assess each vital sign value and categorize either as clinically significant (CS) or not clinically significant (NCS).

Temperature values recorded as °F will be summarized as °C using the function below:

$$°C = (°F - 32) \times \frac{5}{9}$$

For body temperature measurements in degrees of Fahrenheit, both °F and °C values and units will be reported in line listings. Body temperature values obtained from different body parts will be summarized separately by measurement location in the order of oral, tympanic and rectal.

The following summaries for vital signs will be provided:

- A summary of each vital sign along with number and percentage of patient with CS vital sign by treatment group and visit.
- A summary of the change from baseline in each vital sign parameter by treatment group and visit.
- A summary of the number and percentage of patients with any CS vital sign value in each vital sign parameter by treatment group.

By-patient listing will be provided for all patient enrolled by visit, including changes from baseline and investigator's interpretations. A separate listing of potentially clinical important vital signs will be provided for assessments with any CS vital sign observation.

ECG

For each time point, an overall interpretation will be recorded by the Investigator as normal, abnormal not clinically significant, or abnormal clinically significant.

A summary of the number and percentage of patients in each category (normal, abnormal NCS and abnormal CS) will be provided by treatment group and visit.

By-patient listing will be provided for all patients enrolled. A separate listing of potentially clinical important ECG readings will be provided for ECG recordings assessed as CS.

4.11.5 **Safety Monitoring (Data and Safety Monitoring Board [DSMB])**

A Data and Safety Monitoring Board (DSMB) will monitor study results, evaluates the treatments for excess adverse effects, determines whether the basic trial assumptions remain valid, judges whether the overall integrity and conduct of the trial remain acceptable, and makes recommendations to the Abivax study team and to the study principal investigator. The justification for the establishment of the DSMB and the grounds for stopping/continuing studies, as well as the DSMB procedures is provided in the DSMB charter.

The DSMB will be responsible for interpreting the results of periodic safety analyses. Tables, listings, and figures (TLFs) provided for the DSMB will be created by the blinded statistical team (biostatisticians and statistical programmers) using dummy treatment codes and will be passed to the unblinded statistical team who will apply the true treatment codes in a secure manner. Blinded and unblinded directories will be maintained and access to the unblinded directory will be restricted to the unblinded team member until database lock and study unblinding. All TLFs (planned and ad-hoc) created for the DSMB will be developed following the guidelines defined in this SAP, as appropriate. Specifications for these outputs will be included and marked in the TLF shells developed to support the clinical study report.

4.12 Determination of Sample Size

For the sample size / power calculation, the following assumptions are made:

- Primary efficacy endpoint response probability for Standard of Care + ABX464: 84 %
- Primary efficacy endpoint response probability for Standard of Care + placebo: 75 %
- Type 1 error probability: 2.5% one -sided.
- 2:1 (ABX464 50mg: placebo) study treatment allocation ratio.
- One interim analysis after approximately 300 patients complete Day 28 assessment or reach end of study: non-binding futility criterion is a conditional power (calculated under observed effect) ≤ 10%.

If the above assumptions hold true, then an initial total sample size of 800 patients will lead to a power of 78%. Sample size re-assessment and potential increase to 1034 patients is described in Section **Error! Reference source not found.**

All sample size calculations were performed using EAST 6.5

4.13 Changes in the Conduct of the Study or Planned Analysis

1) As part of data and safety monitoring per protocol, a data and safety monitoring board (DSMB) meeting held on 04 March 2021 concluded to study futility and recommended study termination. As sequel to DSMB recommendation sponsor terminated the study due to futility and initiated the

reporting of study result in an abbreviated manner. In accordance with this decision the following changes to the planned analyses are being introduced.

Efficacy results and related analyses are not in the scope of SAP (Section 1). Consequently, the following endpoint will not be derived and/or analyzed:

i) Primary endpoint defined as:

Rate of patients who do not require use of high-flow oxygen (use of high-flow oxygen being defined as settings of 3 L/min or greater AND with at least one SpO2 measurement < 92%, with or without O2 supplementation) or, invasive or non-invasive mechanical ventilation (IMV and NIV, respectively) within 28 days and who are alive at the end of the 28 days period.

ii) Secondary endpoint defined as:

Rate of patients hospitalized, Time to hospitalization from baseline, Number of days at the hospital from admission to discharge;

Seven-point ordinal scale: By visit summaries for percentage of patients in each severity category and Change from baseline in the scale rank, Time to improvement of one level in 7-point ordinal scale;

% change and AUC over time of oxygen saturation measured by daily pulse oximetry before hospitalization;

Rate of patients with SpO2 ⩽94% and rate of patients with SpO2 ⩽92% at Day 28;

Change from enrolment in inflammatory markers in plasma (i.e. MCP-1, MIP-1 α, G-CSF, IL-1b, IL-2, IL-6, IL-7, IL-10, IL-17, INFg and TNFa) and in immune phenotype and assessment of cell-activation markers in PBMCs at D14, D28;

Rate of patients requiring oxygen supplementation, Time to assisted ventilation and oxygen supplementation (log rank) from baseline, Number of days of assisted ventilation, Number of days of oxygen supplementation;

Change from baseline in microRNA-124 levels in total blood (PAXgene®) at D0, D7 and D28;

AUC and % of change from enrolment in CRP, Troponin I & T and D-dimer levels;

Time to death and mortality rate (all causes, and Covid-19 related);

SARS-CoV-2 virus in nasopharyngeal sample and/or in blood at Day 0, 7 (hospitalized patients), 14, 21, and 28;

Change in SpO2 values from D0 to D14 in the outpatient's population,

Rate of participants deceased during the course of the study and follow-up, and time to event (in weeks).

i) Exploratory endpoints defined as:

Central blinded review of the hospitalization discharge CT-Scans for descriptive analysis with regards to the disease severity and outcomes.

Change from last dosing day in the Medical Research Council (MRC) dyspnea scale in the hospitalized patient's population according to treatment group.

Optional: Change from last dosing day in Pulmonary Function Tests (PFT) (Forced Expiratory Volume (FEV) and slow and forced Vital Capacity (VC)) and Carbon Monoxide Diffusing Capacity (CMDC) tests in the hospitalized patient's population according to treatment group.

2) Study day definition is changed as the date of Visit 1 is defined as Day 1 not Day 0 as it is in the protocol. All other study days will be labeled relative to Day 1.

5 REFERENCES

Dandan Wu, Xuexian O. Yang. TH17 Responses in Cytokine Storm of COVID-19: An Emerging Target of JAK2 Inhibitor Fedratinib. Journal of Microbiology, Immunology and Infection, https://doi.org/10.1016/j.jmii.2020.03.005.

Guo, Y., Cao, Q., Hong, Z. et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Military Med Res 7, 11 (2020). https://doi.org/10.1186/s40779-020-00240-0.

Hoffmann, M. et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor; Published: March 05, 2020 DOI: https://doi.org/10.1016/j.cell.2020.02.052.

Mehta, P et al. COVID-19 : consider cytokine storm syndromes and immunosuppression (2020), https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext.

6 APPENDICES

6.1 Prohibited Medications

Treatment Name	Product Code
ABATACEPT	055144 01 001
ABETIMUS	067143 01 001
ADALIMUMAB	016129 01 001
AFELIMOMAB	082507 01 001
ALEFACEPT	016135 01 001
ALEMTUZUMAB	012686 01 001
ALOSETRON	014828 01 001
ANAKINRA	013451 01 001
APREMILAST	072886 01 001
AZATHIOPRINE	000015 01 001
BARICITINIB	078365 01 001
BASILIXIMAB	014111 01 001
BEGELOMAB	087408 01 001
BELATACEPT	056772 01 001
BELIMUMAB	063865 01 001
BRIAKINUMAB	064977 01 001
BRODALUMAB	072962 01 001
CANAKINUMAB	063567 01 001
CERTOLIZUMABPEGOL	088254 01 001
CYCLOSPORINE	005497 01 001
CIPROFLOXACIN	006972 01 001
CLADRIBINE	011748 01 001
DACLIZUMAB	014451 01 001
DIMETHYLFUMARATE	008726 04 001
DULOXETINE	017493 01 001
ECULIZUMAB	056993 01 001
EFALIZUMAB	016270 01 001
EMAPALUMAB	147805 01 001

Treatment Name	Product Code
ENOXACIN	007067 01 001
ESOMARAAZOLE	014793 01 001
ETANERCEPT	014906 01 001
EVEROLIMUS	015069 01 001
FINGOLIMOD	017897 01 001
FLUVOXAMINE	006152 01 001
GLATIRAMER	014109 01 001
GOLIMUMAB	062611 01 001
GUSELKUMAB	083426 01 001
GUSPERIMUS	015708 01 001
INFLIXIMAB	014456 01 001
INSULIN ASPART;INSULIN ASPART PROTAMINE	014758 05 001
INTERFERON	005968 01 001
IXEKIZUMAB	073399 01 001
LEFLUNOMIDE	014148 01 001
LENALIDOMIDE	016801 01 001
ACEMIN [LISINOPRIL]	008940 01 001
METHADONE	000689 01 001
METHOTREXATE	001138 01 001
MONTELUKAST	013626 01 001
MUROMONAB	008924 01 001
MYCOPHENOLICACID	012751 01 001
NATALIZUMAB	017549 01 001
OCRELIZUMAB	055060 01 001
OZANIMOD	090204 01 001
PANTAC	012632 04 001
PARACETAMOL	000200 01 001
PARACETOMOL	000200 01 001
PHENYTOIN	000174 01 001
PIRFENIDONE	062251 01 001

Treatment Name	Product Code
POMALIDOMIDE	068192 01 001
RAMELTEON	054956 01 001
RANTAC	005508 02 001
RIFAMPIN	001469 01 001
RILONACEPT	061986 01 001
ROPINIROLE	012429 01 001
SARILUMAB	072221 01 001
SECUKINUMAB	072446 01 001
SILTUXIMAB	063318 01 001
SIROLIMUS	014591 01 001
SIRUKUMAB	072099 01 001
TACROLIMUS	012199 01 001
TASIMELTEON	063036 01 001
TERIFLUNOMIDE	057464 01 001
THALIDOMIDE	000774 01 001
THEOPHYLLINE	000122 01 001
TILDRAKIZUMAB	082047 01 001
TIZANIDINE	007407 01 001
TOCILIZUMAB	017591 01 001
TOFACITINIB	079186 01 001
USTEKINUMAB	062576 01 001
VEDOLIZUMAB	062574 01 001
VOCLOSPORIN	062225 01 001
WARFARIN	000148 01 001

6.2 Schedule of Assessments

Table 3 Schedule of Assessments

Study Period		Treatment						Unscheduled Visit	Follow-Up (FUP)	
Visit		Visit 1 [13]	Remote Medical Monitoring of Outpatients to be done every 2 days between	Visit 2	Visit 3	Visit 4	Visit 5 (EoT)		Visit 6 Safety FUP	V7 – Long-term FUP
Day		Day 0		D7 for hosp. Patients/and potentially outpatients	Day 14	Day 21	Day 28		Day 48	3 months post last SD intake
GENERAL										
	Signed inform consent form collection	X								
	Check of IN/EX Criteria	X								
	Demographic data collection	X								
	Medical History	X								
	Current medications	X	X	X	X	X	X	X	X	
	7-point Ordinal scale	X		X	X	X	X		X	X
PHYSICAL EXAMS										
	Physical Examination (including vital signs) [1]	X		X	X	X	X	X	X	
	Oxymeter and patient diary dispensation/collection	X			X					
	Remote monitoring of body temperature, SPO2 and Clinical Signs of COVID-19		Monitoring every 2 days between D2 and D14							
	Outpatients mortality status [12]									
	Body Weight (kg) & Height (cm) measurements [2]	X								

Study Period	Treatment							Follow-Up (FUP)	
Visit	Visit 1 [13]	Remote Medical Monitoring of Outpatients to be done every 2 days between	Visit 2	Visit 3	Visit 4	Visit 5 (EoT)	Unscheduled Visit	Visit 6 Safety FUP	V7 – Long-term FUP
Day	Day 0		D7 for hosp. Patients/and potentially outpatients	Day 14	Day 21	Day 28		Day 48	3 months post last SD intake
ECG [3]	X		X	X	X	X	X	X	
ANALYSIS TO BE PERFORMED LOCALLY									
Blood Pregnancy test (WOCBP) [4]	X								
Hematology + Biochemistry [5]	X		X	X	X	X	X	X	X [10] (Hb only)
BIOBANKING									
Plasma (CRP, Troponin I & T, D-Dimer [6])	X		X	X	X	X	X		
Immunophenotyping and cells activation markers [7]	X			X		X	X		
Blood sample Cytokines [8]	X			X		X	X		
Nasopharyngeal and blood samples for viral load assessment	X		X	X	X	X	X		
Samples for miRNA-124 (Blood PAXgene tube)	X		X			X			
IMAGING									
Chest CT-SCANS [9]	X								
RESPIRATORY FUNCTION EVALUATION [10]									
Medical Research Council Dyspnea scale	For hospitalized patients only – to be performed at discharge								X
Spirometry	(For hospitalized patients only – to be performed at discharge)								(X)
CMDC	(For hospitalized patients only – to be performed at discharge)								(X)
TREATMENT ALLOCATION									
Randomization	X								

Study Period	Treatment							Follow-Up (FUP)	
Visit	Visit 1 [13]	Remote Medical Monitoring of Outpatients to be done every 2 days between	Visit 2	Visit 3	Visit 4	Visit 5 (EoT)	Unscheduled Visit	Visit 6 Safety FUP	V7 – Long-term FUP
Day	Day 0		D7 for hosp. Patients/and potentially outpatients	Day 14	Day 21	Day 28		Day 48	3 months post last SD intake
ABX464/placebo treatment dispensation [11]	X								
ABX464/placebo treatment accountability						X			
SAFETY									
Adverse Events recording	X	X	X	X	X	X	X	X	

[1] Physical examinations: a complete physical examination will be performed at D0, at the End of treatment visit (EoT), and at D48. Only differences from baseline will be reported at every other visit.
[2] Body Weight and Height: Body weight and height will be measured at D0 for BMI assessment.
[3] ECG: A 12-Leads ECG will be performed at every on-site study visit.
[4] Blood pregnancy test: Applicable to all women of childbearing potential at D0 and at D48. In order not to limit the patient enrollment a urine pregnancy test can be performed in addition if the blood test result is not available at the time of randomization.
[5] Hematology + Biochemistry: samples to be taken at every on-site study visit (except D7 for outpatients if not possible) and analyzed locally.
[6] CRP, Troponin I & T and D-Dimer: samples to be taken at every on-site study visit (except D7 for outpatients if not possible) and sent to central laboratory for biobanking purpose.
[7] Immunophenotyping and cells activation markers: samples will be taken in selected sites and for approximately 100 patients.
[8 Blood sample Cytokines: samples will be taken in all sites for all patients.
[9] Chest CT-scan: procedure concerns hospitalized patients only. (whenever the hospitalization occurs during the course of the study). Images taken at discharge (± 7 days) will be assessed locally, then collected and sent to a blinded central reader for descriptive analysis of the lesions. If available at D0, Baseline CT scans of hospitalized patients will be sent to Central Reader for comparison purpose.
[10] Respiratory function evaluation: This evaluation will be performed only in patients who were hospitalized during the course of the study. For these patients the MRC Dyspnea assessment scale must be used at discharge and 3 months after last study drug intake. For sites having adequate facilities a PFT (FEV1 and slow and forced Vital Capacity) and a Carbon Monoxide Diffusing Capacity (CMDC) evaluation will be performed at discharge and 3 months after last study drug intake (optional assessments). For this last test, a blood sample for hemoglobin assessment must be taken within 48hrs prior to the CMDC test.
[11] ABX464/placebo treatment dispensation: treatment dispensation will be allowed once all the selection criteria are confirmed, including laboratory assessments for patients' eligibility confirmation.

Study Period	Treatment							Follow-Up (FUP)	
Visit	Visit 1 [13]	Remote Medical Monitoring of Outpatients to be done every 2 days between	Visit 2	Visit 3	Visit 4	Visit 5 (EoT)	Unscheduled Visit	Visit 6 Safety FUP	V7 – Long-term FUP
Day	Day 0		D7 for hosp. Patients/and potentially outpatients	Day 14	Day 21	Day 28		Day 48	3 months post last SD intake

[12] Outpatients mortality status: For patients not hospitalized during the course of the study, a phone contact will be done 3 months after the last study drug intake to collect their mortality status.

[13] V1: Visit 1 can be splitted into 2 separated visits for outpatients to follow site organization and quarantines requirement. However, the interval between these 2 visits cannot exceed 48 hours to ensure patients start the study treatment at an early stage of the disease. Date of first intake of study drug will be considered as D0.

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Reason for signing: Approved	Name: Istvan Nemeth Role: Biostatistics Date of signature: 16-Jun-2021 10:24:28 GMT+0000

Reason for signing: Approved	Name: Zeina KaramAbsi Role: Medical Monitoring Date of signature: 16-Jun-2021 11:32:58 GMT+0000

Reason for signing: Approved	Name: Paul Gineste Role: Clinical Operations Date of signature: 16-Jun-2021 12:09:29 GMT+0000

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