Cover page:

Clinical Trial Protocol: A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of TJ003234 in Subjects with Severe Coronavirus Disease 2019 (COVID-19)

(Protocol Number TJ003234COV201)

NCT: NCT04341116

Document Date: 23 Sept 2021

Clinical Trial Protocol

A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of TJ003234 in Subjects with Severe Coronavirus Disease 2019 (COVID-19)

This study will be conducted according to this protocol, including protocol amendments and in compliance with Good Clinical Practice, the ethical principles, and other applicable regulatory requirements.

Protocol number:	TJ003234COV201
Study drug:	TJ003234
Indication:	Severe Coronavirus Disease 2019 (COVID-19)
Sponsor:	I-Mab Biopharma Co., Ltd.
Address:	Suite 802, West Tower, 88 Shangke Road
	Pudong New District
	Shanghai 20120, China
Protocol version	9.0
Date	23 September 2021

These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.

Sponsor Approval

I have read this protocol and approve it:

DocuSigned by:
Claire Xu 9/23/2021 | 3:48:32 PM EDT
Signer Name: Claire Xu
Signing Reason: I approve this document
Signing Time: 9/23/2021 | 3:48:29 PM EDT
694B2B1EEED8462B8E8C4CD8F1AD4794

Claire (Cong) Xu, MD, PhD Date

US Site Head

Sponsor Contact Information

Name	Title/Role	Contact Information
Claire Xu, MD, PhD	Study Director/Medical Monitor	Phone: 317-755-8242 Email: claire.xu@i-mabbiopharma.com
Elizabeth Lindner	Director, Clinical Project Management	Phone: 856-261-4470 Email: Elizabeth.lindner@i-mabbiopharma.us
Andria White	Clinical Project Manager	Phone: 631-356-0091 Email: Andria.White@i-mabbiopharma.us

If any contact information changes during the course of the study, written notification will be provided to the Investigator and IRB/IEC, per requirements. A protocol amendment will not be required in this case.

Investigator Agreement

I have read the protocol and agree to conduct the study as described herein:

_____
Principal Investigator (Printed)

_____
Principal Investigator (Signature) Date

_____
Clinical Site

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from I-Mab Biopharma representatives, the Declaration of Helsinki, ICH Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

Table of Contents

List of Tables

List of Figures

Protocol Synopsis

Protocol Title:

A Phase 2/3 Randomized, Double-blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of TJ003234 in Subjects with Severe Coronavirus Disease 2019 (COVID-19)

Objectives:

Primary Objective:

To evaluate the efficacy and safety of TJ003234 in subjects with severe COVID-19 with supportive care.

Secondary Objectives:

- To evaluate the effects of TJ003234 on cytokines in subjects with severe COVID-19.
- To assess the pharmacokinetics (PK) and immunogenicity potential of TJ003234 when administered as a single dose IV infusion in subjects with severe COVID-19.

Endpoints:

Primary Efficacy Endpoints:

Proportion (%) of subjects who are alive and free of mechanical ventilation at Day 30 among subjects who are non-mechanical ventilated at baseline.

Key Secondary Efficacy Endpoints:

- Proportion (%) of subjects recovered by Day 14. Recovery is defined as the subject scoring a 3, 2, or 1 on the 8-category ordinal scale below by Day 14 and subsequently does not progress to a score ≥ 4 for the remainder of the study. If a subject scores 3 at baseline, this subject is considered to be recovered if this subject's score improves to 1 or 2 by Day 14.

8, death; 7, ventilation in addition to extracorporeal membrane oxygen (ECMO), continuous renal replacement therapy (CRRT) or pressors; 6, intubation and mechanical ventilation; 5, non-invasive mechanical ventilation (NIV) or high-flow oxygen; 4, hospitalization with oxygen by mask or nasal prongs; 3, hospitalization without oxygen supplementation; 2, limitation of activities, discharge from hospital; and 1, no limitation of activities, discharge from hospital.

- Proportion (%) of subjects recovered by Day 30. Sustained recovery is defined as the subject scoring a 3, 2, or 1 on the 8-category ordinal scale as defined in the key secondary endpoint by Day 30 and subsequently does not progress to a score ≥ 4 for the remainder of the study. If a subject scores 3 at baseline, this subject is considered to be recovered if this subject's score improves to 1 or 2 by Day 30.
- All-cause mortality rate on Day 30.

Secondary Efficacy Endpoints:

- Time to sustained recovery among subjects alive by Day 30 [Time Frame: Day 1 through Day 30]: Day of sustained recovery is defined as the first day on which the recovered subject scores 3, 2 or 1 and maintains such score through Day 30 from the 8-category ordinal scale as defined in the key secondary endpoint. If a subject is scored at 3 at baseline, day of recovery is defined as the day on which this subject's score improves to 1 or 2 and maintains such score through Day 30.
- Length of hospitalization.

Exploratory Efficacy Endpoints:

- Improvement in clinical status (Day 7, Day 14 and Day 30)
- Sequential Organ Failure Assessment score (SOFA score) (Day 7 and Day 14 from the day of dosing)
- Change from baseline in PaO2/ FiO2 (Day 7 and Day 14 from the day of dosing)
- Length of time to normalization of oxygen saturation which is defined as SpO2≥94% sustained minimum 24 hours
- Percentage of subjects requiring mechanical ventilation at Day 7 and Day 14
- Change from baseline in serum cytokines, e.g. IL-1RA, IL-1β, IL-2, IL-6, IL-7, IL-10, GCSF, GM-CSF, CCL2, CCL3, CCL17, CXCL10, TNF-α and IFN-γ, etc. (Day 2, Day 3, Day 5, Day 7, and Day 14 from the day of dosing)
- Change from baseline in D-dimer, cardiac troponin, LDH, and ferritin levels (Day 7 and Day 14 from the day of dosing)
- Peripheral blood neutrophils-to-lymphocyte ratio (NLR)

Safety Endpoints:

- Treatment-emergent Adverse events evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Criteria (CTCAE) (version 5.0),
- Changes from baseline in clinical laboratory parameters, physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), and radiographic lung imaging.

Pharmacokinetic and Immunogenicity Endpoints:

- Serum concentration of TJ003234 (Day 1 predose, Day 1 End of Infusion, Day 7 and Day 14)
- Incidence and titer of anti-drug antibodies (ADA) (Day 1 predose, Day 14)

Study Design:

This is a phase 2/3 randomized, double-blind, placebo-controlled, multi-center trial to evaluate the safety and efficacy of TJ003234 administered as an intravenous (IV)

infusion in subjects with severe COVID-19 under supportive care, and to assess the effect of TJ003234 on the levels of cytokines. The study will be conducted in two parts.

Part 1:

Part 1 is designed as a randomized, double-blind, placebo-controlled, 3-arm, parallel-group study to evaluate the safety of TJ003234 in subjects with severe COVID-19. Potential subjects will be screened to assess their eligibility to enter the study within 3 days prior to study drug administration. A total of 24 eligible subjects will be randomized at a ratio of 1:1:1 to receive either a single dose of 3 mg/kg TJ003234, a single dose of 6 mg/kg TJ00324 or placebo, administered by IV infusion. Before and after the treatment, all subjects will be allowed to receive supportive care and/or additional treatments for COVID-19 and its complications per the Investigator. Up to twenty-four subjects will be enrolled in Part 1. If no more than 2 out of 8 subjects experience a Grade ≥3 treatment-related adverse event (AE) within 7 days of the subjects receiving the study drug in either TJ003234 arm and no more than 4 out of 16 subjects experience a Grade ≥3 treatment-related AE within 7 days of the subjects receiving the study drug in both TJ003234 arms combined, Part 2 will be initiated. The end of Part 1 is defined as 30 days after the last subject is dosed, or until study termination.

Part 2:

Part 2 is designed as a randomized, double-blind, placebo-controlled, 2-arm, parallel-group study to evaluate the safety and efficacy of TJ003234 in subjects with severe COVID-19. Part 2 contains two phases, the first phase, Phase 2, will enroll 120 subjects and the second phase, Phase 3, will enroll approximately 450 subjects. The data collected from Phase 2 will be used to make decision for Phase 3 and may be used to re-estimate sample size of Phase 3 portion. Potential subjects will be screened to assess their eligibility to enter the study within 3 days prior to the first dose administration. A total of 570 eligible subjects will be randomized at a ratio of 2:1 to receive either a single dose of TJ003234 or placebo, administered by intravenous infusion. Subjects in Part 2 Phase 2 will receive either a single dose of 6 mg/kg TJ003234 or placebo. Subjects in Part 2 Phase 3 will receive either a single dose of 10 mg/kg TJ003234 or placebo. Randomization will be stratified by age and use of remdesivir. Before and after the treatment, all subjects will be allowed to receive supportive care and/or additional treatments for COVID-19 and its complications per the Investigator.

Follow-up Period:

After study drug administration, all subjects will enter a follow-up period and will be evaluated for safety and efficacy for 30 days after the last dose of study drug. Subjects will be followed for 30 days following the day of dosing (Day 1), or until withdrawal of consent, lost to follow-up, or death.
End of study is defined as Day 30 from the day of enrollment of the last subject, or study termination.

Safety Evaluations:

All adverse events will be collected from the day of informed consent to Day 30.

All subjects who received the study drug will be included in the safety analysis. The CTCAE Version 5.0 will be used as the criteria for safety evaluation.

The safety evaluations will be performed at Screening, Day 1 predose (baseline), Day 7, Day 14 and Day 30.

Safety endpoints will include treatment-emergent adverse events, changes from baseline in physical examinations, clinical laboratory parameters, vital sign measurements, pulse oximetry, 12-Lead ECG, and radiographic lung imaging.

Clinical laboratory parameters will include complete blood count (CBC), serum chemistry (including Lactate Dehydrogenase (LDH)), coagulation profile, troponin, arterial blood gas analysis, C-reactive Protein (CRP), and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) diagnostic test by polymerase chain reaction (PCR) or other commercial or public health assay.

Radiographic lung imaging will include lung computed tomography (CT) or lung X-ray.

Efficacy Evaluations:

The efficacy evaluations in this study will be performed based on clinical status (8-category ordinal scale), sequential organ failure assessment (SOFA) score, and PaO2/ FiO2. They will be evaluated from Day 1 predose (baseline) to Day 30. In addition, the subjects will be assessed for all-cause mortality and need for mechanical ventilation.

Changes from baseline in serum cytokines including IL-1RA, IL-1β, IL-2, IL-6, IL-7, IL-10, GCSF, GM-CSF, CCL2, CCL3, CCL17, CXCL10, TNF-α and IFN-γ, etc. will be measured on Day 1 pre-dose, and Days 2, 3, 5, 7, and 14 post-dose.

Sample Size:

This is a 2-part study. Part 1 will enroll about 24 subjects to establish the safety profile of single dose of 3 mg/kg and 6 mg/kg of TJ003234 in subjects with severe COVID-19 before moving to Part 2. Part 2 plans to enroll 570 subjects. Eligible subjects will be randomized to TJ003234 or placebo with a ratio of 2:1. Assuming mechanical ventilation free rates by Day 30 are 77% in the control arm and 88% in the treatment arm, with 10% drop-out rate, a total of 120 subjects are required based on a 2-sided alpha level of 0.2 and 80% power in the Phase 2 portion, and a total of 450 subjects are required based on a 2-sided alpha level of 5% and 80% power in the Phase 3 portion.

Scientific Rationale for Study Design:

GM-CSF, as a key upstream trigger factor in the inflammatory cytokine cascade, can enhance the effects of neutrophils and macrophages, produce inflammatory cytokines and activate the phagocytosis. In addition, GM-CSF is also an important cytokine that induces the polarization of monocytes to the inflammatory M1 phenotype and promotes the activation of macrophages, and the macrophages secrete a large number of inflammatory cytokines such as IL-6 and TNF-α, to involve in tissue inflammation (Hamilton, 1980). The strong proinflammatory effects of GM-CSF make it a promising target in acute inflammatory conditions where elevated GM-CSF has been implicated in orchestrating a cytokine storm. At least three such syndromes share immunological and pathologic features of a cytokine storm: chimeric antigen receptor (CAR)-T cell therapy related cytokine release syndrome (CRS), macrophage activation syndrome (MAS) and most recently, acute respiratory distress syndrome (ARDS) in severe coronavirus disease (COVID-19) cases caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).

In the recent COVID-19 epidemic caused by the coronavirus SARS-CoV-2 in China, approximately 15-30% of severe COVID-19 patients developed ARDS (Wang, 2020; Huang, 2020; Chen, 2020; Guan, 2020). Without intervention, the clinical course is expected to be dire for severe COVID-19 patients. Therefore, there is a huge unmet

medical need of therapy for severe COVID-19 patients. At present, there is no specific immune modulating therapy for severe COVID-19 patient.

The clinical features (Huang, 2020) and immunopathology (Xu, 2020) of patients with COVID-19 in China have now been reported, and they remarkably resembled those found in SARS (Channappanavar, 2017). Common features among COVID-19 patients, particularly those seriously or critically ill, included lymphopenia and significantly elevated levels of inflammatory cytokines including IL-1, IL-7, IL-8, IL-9, IL-10, basic FGF, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1A, MIP-1B, PDGF, TNF-α, and VEGF. (Huang, 2020). Massive production of IL-6, CRP, D-dimer and ferritin were also observed, which are all indicative of cytokine storm (Wang, 2020). Importantly, lung pathology revealed heavy interstitial lymphocytic infiltrates along with diffuse alveolar damage with fibromyxoid exudates, multinucleated giant cells and hyaline membrane formation, indicative of ARDS (Xu, 2020). Interestingly, these pathological features and lung CT imaging characteristics are also remarkably similar to those reported for a subset of Systemic Juvenile Idiopathic Arthritis (JIA) patients that developed MAS that led to severe immunopathology and lung disease (Schulert, 2019).

It seems evident from the recent reports that severe COVID-19 bears all the hallmarks of a cytokine storm instigated by exuberant immune cells producing GM-CSF and IL-6. They drive aberrant monocyte and T cell activation which in turn produce more cytokines and chemokines in a feed forward cycle that culminates in profound tissue injury, airway constriction, vascular collapse and organ failure (Zhou, 2020). Peripheral blood mononuclear cell (PBMC) immunophenotyping showed an abundance of highly active GM-CSF-producing T helper cells and pathogenic monocytes in COVID-19 patients (Xu, 2020; Zhou, 2020). A recent study published in *Blood* showed that GM-CSF antibodies have been demonstrated to effectively inhibit the cytokine storm caused by CAR-T cell therapy and reduce the levels of a series of inflammatory factors such as IFN-g, IL-6, MCP-1, MIP-1 in preclinical experiments. In addition, it can control the infiltration of immune cells such as T cells and macrophages into the central nervous system, and effectively inhibit the generation of neurotoxicity (Sterner et al., 2019). Compared to tocilizumab that has been widely used to treat cytokine storm caused by CAR-T cells, GM-CSF antibodies may have better efficacy, especially in regulating the broad spectrum of cytokines and inhibiting neurotoxicity. Therefore, two clinical trials will be conducted to evaluate the therapeutic effects of GM-CSF antibodies or GM-CSF receptor antibodies on CAR-T cell-induced side effects such as cytokine storm and neurotoxicity (Gilead, 2020). Currently, based on the experience of IL-6R antibody tocilizumab in managing CAR-T induced CRS, tocilizumab is being tested for reducing cytokine storm and its complications in a clinical trial of COVID-19 patients in China (Chinese Clinical Trial Registry, n.d.). GM-CSF neutralizing antibody such as TJ003234 may also have the potential to prevent or curb cytokine storm and immunopathology and thus earn more time for viral clearance, which may improve the overall clinical outcome of COVID-19 severe patients.

Justification for Dose:

In this study, the dose of TJ003234 has been predicted based on the results of safety, pharmacokinetics and pharmacodynamics from a single ascending dose study in healthy subjects, preclinical data, the safety data of similar GM-CSF antibodies in patients with rheumatoid arthritis, as well as the data of IL-6R antibody tocilizumab for treatment of cytokine storms. For TJ003234, a single dose escalation study in 32 healthy subjects has

been completed. No dose limiting toxicity (DLT) was observed in the 0.3 mg/kg, 1 mg/kg, 3 mg/kg and 10 mg/kg dose groups. The maximum tolerated dose (MTD) was not reached. The half-life of TJ003234 was approximately 3 weeks and plasma concentrations increased proportionally with the dose over the range 0.3 mg/kg to 10 mg/kg. Pharmacodynamics showed similar levels of inhibition of ex-vivo GM-CSF-activated phosphorylated signal transducer and activator of transcription 5 (pSTAT5) at doses of TJ003234 3 mg/kg and 10 mg/kg. Inhibition of more than 90% was reached at 4 hours after dosing and was maintained for 2 weeks (full clinical study report submitted to FDA in January 2020).

The dosing regimen of TJ003234 in the Part 2 Phase 3 trial is amended as 10 mg/kg TJ003234 or placebo based on the observed efficacy, safety, and PK data in the completed Part 2 Phase 2 study. In Part 2 Phase 2 study with patients with Covid-19, improved efficacy over the placebo arm was observed with an acceptable toxicity profile of TJ003234. At the same time, increased clearance of TJ003234 (0.02 L/hr in patients with Covid-19 compared to 0.009 L/hr in healthy subjects) was observed at a single dose of 6 mg/kg TJ003234, with a shorter half-life (6 days) than in healthy subjects (3 weeks). Therefore, a single dose of 10 mg/kg is expected to further improve the magnitude of efficacy improvement by providing higher exposure than that of 6 mg/kg dose in Covid-19 patients. Based on the observed PK data, the exposure of a single dose of 10 mg/kg TJ003234 in patients with Covid-19 is expected to be lower than that in healthy subjects. Therefore, an acceptable safety profile is expected to be maintained, as the 10 mg/kg has been tested in healthy subjects with excellent safety profile. According to the preclinical toxicology study (once weekly (Q1W) for 4 weeks), the No-Observed-Adverse-Effect Level (NOAEL) dose in Cynomolgus monkeys was 60 mg/kg. Since molecular weight of TJ003234 is >100,000 Da (146KDa) and administered intravenously, according to FDA guidance stating that proteins administered intravascularly with molecular weight >100 KDa should be normalized to mg/kg as an exception to mg/m^2 scaling approach (CDER, 2005), the calculated Human equivalent dose (HED) based on NOAEL is also 60 mg/kg.

GM-CSF antibodies have been reported to be well tolerated in clinical trials. Namilumab and KB003 are drugs with the same mechanism of action as the study drug and both were well tolerated at doses of 5-6 mg/kg (Huizinga et al., 2017). The Phase IIb clinical trial of mavrilimumab, which is an antibody of GM-CSF receptor and has a similar mechanism of action as the study drug, showed no adverse reactions in the lung (Burmester et al., 2017). The autoantibodies of GM-CSF are associated with the development of idiopathic autoimmune pulmonary alveolar proteinosis (PAP). There is a theoretical risk of developing PAP when therapeutic antibodies targeting GM-CSF are used. Non-clinical studies of mavrilimumab, a compound targeting GM-CSF receptor, showed that macrophage change in lung tissues was only observed in studies with dosing lasting more than 11 weeks (Ryan et al., 2014). Therefore, it is believed that PAP is a long-term chronic development process and, the risk of PAP developed from drug exposure after a single dose is most likely to be low. In addition, we closely monitored pulmonary function up to 90 days and no clinically meaningful changes of pulmonary function were observed in the single dose escalation study (full clinical study report submitted to FDA in January 2020). Taken together with the safety data in human and preclinical studies, we believe that a single dose of 3 mg/kg and 6 mg/kg TJ003234 will be safe in the patient population.

Preclinical pharmacodynamics showed a treatment effect of <50% (as measured by an inhibitory effect on the GM-CSF/GM-CSFR signaling pathway) at a single intravenous

infusion dose of 3 mg/kg in the CIA (type II collagen-induced arthritis) model in cynomolgus monkeys. The results from the in vitro monocyte activation assay to mimic the COVID-19 viral stimulation of primary monocytes confirmed that treatment of 10 μg/ml TJ003234 suppressed the pro-inflammatory cytokine production and activation marker expression, indicating that the dose of 3 mg/kg may be efficacious since the trough concentration of a single dose of 3 mg/kg exceeds 10 μg/ml in the Phase I clinical trial. On theoretical grounds, the GM-CSF levels will further increase in COVID-19 patients with cytokine storms compared to healthy individuals and patients with autoimmune diseases. This hypothesis has been confirmed by the clinical data of tocilizumab. The mean peak concentration of tocilizumab in patients with cytokine storms caused by CAR-T was 41% lower than that in patients with systemic JIA, suggesting that tocilizumab was eliminated more rapidly in patients with cytokine storms (Le et al., 2018). Therefore, in order to better assess the dose response of TJ003234 in COVID-19 severe patients, and determine an optimal dose for further development, we plan to include an additional dose level of 6 mg/kg TJ003234. Based on the PK from healthy adults, TJ003234 PK appears to be linear and we expect that a single dose of 6mg/kg may produce two-fold of drug exposure following a single dose of 3 mg/kg TJ003234, which will remain within the range of drug exposure tested to be safe in the first-in-human (FIH).

Overall, the totality of the data from the non-clinical data and clinical data from the single ascending dose escalation study supports **3 mg/kg and 6 mg/kg** as a safe dose with potential efficacy to be administered in COVID-19 patients. Furthermore, the observed efficacy, safety, and PK data in the completed Part 2 Phase 2 study support a single dose of 10 mg/kg TJ003234 in the subsequent Part 2 Phase 3 trial as a safe dose with further improved efficacy.

Inclusion and exclusion criteria:

Inclusion criteria (To be included in the study, subjects must meet all of the following criteria):

1. Age: 18 years or older (including 18 years); male or female
2. Laboratory-confirmed SARS-CoV-2 or COVID-19 infection as determined by polymerase chain reaction (PCR) or other commercial or public health assay.
3. Bilateral lung infection confirmed by imaging.
4. Severe disease that meets one of the following conditions:
    i. At rest, finger blood oxygen saturation ≤ 93% or PaO2/FiO2 ≤ 300 mmHg; OR
    ii. Requiring high flow oxygen ≥15L/min
5. Subjects or legally authorized representatives (LARs) who are willing to participate in this study and sign the informed consent voluntarily.
6. Be willing to follow the contraception guidelines in Appendix 1
7. Subject has been hospitalized for no more than 5 calendar days at the time of screening.

Exclusion Criteria (Subjects who meet any of the following criteria will be excluded from the study):

1. Any previous and/or current clinically significant disease or condition that has not been stable within 3 months prior to enrollment, or acute illness, planned medical/ surgical procedure, or any trauma that occurred within 2 weeks prior to enrollment, which, in the opinion of the investigator, may place the subject at risk if participating in the study, or may interfere with the assessment of the study drug or confound interpretation of the study results, or affect the patient's ability to participate in the study independently.
2. ***Applies to Part 1 Only:*** Chronic obstructive pulmonary disease (COPD) and moderate/severe asthmatic patients requiring inhaled corticosteroid, long-acting beta-adrenergic agonists, long-acting anticholinergics, or long-term oxygen therapy. Mild asthmatic patients treated with short-acting beta-adrenergic agonists and/or low dose of inhaled corticosteroid and/or long-acting beta-adrenergic agonists are considered eligible. Please refer to Appendix 4 for inhaled cortiscoteroids dose guidance.
3. Pulmonary interstitial disease, pulmonary alveolar proteinosis, and pulmonary granulomatosis.
4. Cardiovascular event in the 3 months prior to study drug administration: acute myocardial infarction or unstable angina pectoris, severe arrhythmia (multiple sources of frequent ventricular premature beat, ventricular tachycardia and ventricular fibrillation); New York Heart Association Classification (NYHA): Class III-Class IV.
5. Severe renal impairment: e.g. eGFR ≤30 ml/min estimated by MDRD equation or have received treatments such as kidney transplantation and dialysis.
6. Subjects that cannot adhere to protocol requirements due to neuropsychiatric disorders.
7. Severe liver disease: e.g. Child-Pugh Score for Cirrhosis as Grade C, elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 × upper limit of normal.
8. Known active or chronic hepatitis B or C infection or human immunodeficiency virus (HIV).
9. Known active tuberculosis (TB), history of incompletely treated TB, suspected or known extrapulmonary TB, suspected or known systemic bacterial or fungal infections.
10. Blood system disorders or routine blood analysis test abnormalities:
    - Hemoglobin < 8 g/dL;
    - Absolute neutrophil count (ANC) <1500 × 10^9/L;
    - Platelets < 50 × 10^9/L.
11. Dependence on glucocorticoid treatment equivalent to methylprednisolone 2 mg/kg/ day or more or long-term use of anti-rejection or immunomodulatory drugs.

12. Subjects that require invasive mechanical ventilation or ECMO.
13. Pregnant or breastfeeding females.
14. Have received any live vaccination within 30 days before dosing.
15. Subjects who, in the opinion of the investigator, are not suitable for participation in this clinical study or will not agree to follow the institution's supportive care protocol. Any condition that, in the opinion of the investigator, may increase the risk associated with the subject's participation in the study or may interfere with the assessment of the study drug or confound the interpretation of the study results.

Criteria for study termination

During the conduct of the study, if the investigator or the sponsor finds that continuation of the trial may cause potential harm to subjects, the decision may be made to terminate the trial after consultation between the investigator, medical monitor and the sponsor.

Statistical Considerations:

Analysis Populations:

Intent-to-treat (ITT) Population: All randomized subjects. This population will be used for the primary analysis for Part 1 and Part 2 phase 2 portion, and sensitivity analysis of primary analysis for Part 2 phase 3 portion.

Modified Intent-to-treat (mITT) Population: All randomized subjects who are non-mechanical ventilated at baseline. This population will be used for the primary analysis for Part 2 phase 3 portion.

Safety Population: Includes all subjects who receive the study drug. This safety population will be used for the analysis of demographic data, baseline characteristics, and safety.

Efficacy-evaluable Population: All subjects in the safety population with at least one post-dose efficacy evaluation.

General Methods:

All data will be summarized by treatment group using descriptive statistics based on the data types. Unless otherwise specified, descriptive statistics for continuous variables will include number of subjects, mean, standard deviation (SD), median, and range. For categorical variables, descriptive statistics including counts and percentages will be reported. Data from Part 1 and Part 2 will be analyzed separately.

Safety Analysis:

Safety and tolerability evaluations will be performed for all subjects in the safety population.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Summary statistics and listings of all the safety data will be provided by treatment group and time points as specified in the schedule of procedures.

Efficacy Analysis:

For each part, efficacy endpoints will be summarized by treatment group with

descriptive statistics based on the ITT / mITT / efficacy-evaluable population. Treatment difference along with the 95% CI will be reported. Subgroup analysis by age at randomization (<60 years, ≥60 years) and use of remdesivir (yes/no) might be performed where data permits.

For the efficacy endpoints in Part 2, the primary endpoint will be analyzed using the exact method. Difference between two arms will be tested by a stratified Cochran–Mantel–Haenszel test (CMH) test using the stratification factors at randomization. Recovery rates by Day 14, recovery rates by Day 30 , and all-cause mortality rate, will be analyzed similarly. Time to recovery among subjects alive by Day 30 will be analyzed by a stratified log-rank test for p-value, and the HR ratio between two arms will be estimated by a stratified Cox proportional hazard model using the stratification factors at randomization.

For the Phase 3 portion, multiplicity will be adjusted by a gatekeeping procedure. If the null hypothesis for the primary endpoint is rejected, then the key secondary endpoints will be tested in the order of: recovery rate by Day 14, recovery rate by Day 30, and all-cause mortality rate by Day 30.

The trial will be considered as successful if the primary endpoint in Phase 3 portion shows a statistically significant improvement in the treatment arm and, as a safety measurement, the all-cause mortality rate in the treatment arm is numerically not higher than that in the control arm.

Independent Data Monitoring Committee (IDMC):

The IDMC is responsible for monitoring safety. The IDMC will be made up entirely of members external to I-Mab. The IDMC charter will contain membership information and a further delineation of responsibilities.

The IDMC may recommend continuing enrollment in one dose arm or to terminate the study for accumulated safety evaluations. The IDMC will provide a recommendation that is made without known bias. I-Mab staff involved in the conduct of the study will be kept blinded before a portion of the study is completed, and the members of the IDMC will not have involvement with the conduct of the study.

Schedule of Procedures

Table 1. Schedule of Procedures

Procedure	Screening period*	Baseline period*	Follow-up period						
	-D3-D1	D1	D2	D3	D5	D7**	D11** ±1	D14** ±2	D30** ±2
Informed Consent	√								
Demographics	√								
Body weight	√								
Medical history, smoking history and medication history, and baseline respiratory support requirements	√	√							
Pregnancy test or FSH test [1]	√								
SARS-CoV-2 diagnostic test [2]	√					(√)		(√)	(√)
Radiographic lung imaging [3]	√	√				√		√	√
Arterial blood gas analysis [4, 16]	√	√				√		√	√
PaO2/FiO2[16]	√	√				√		√	√
Physical Examination	√	√	√	√	√	√		√	√
Pulse Oximetry [5]	√								
Clinical status [6]		√				√		√	√
Vital signs	√	√	√	√	√	√	√	√	√
12-lead ECG [7]	√	√				√		√	√
Routine complete blood count, blood biochemistry test, coagulation assessment [8]	√	√	√	√	√	√		√	√
Urinalysis [9]	√	√	√	√	√	√		√	√
Troponin		√				√		√	
C-reactive protein, LDH, serum ferritin	√	√	√	√	√	√		√	√
Cytokine levels [10]	√	√	√	√	√	√		√	√
SOFA (Sequential Organ Failure Assessment score) [11, 16]		√				√		√	√
Review subject eligibility	√	√							
Randomization		√							
Dosing [12]		√							
Pharmacokinetic Sampling [13]		√				√		√	√
Anti-drug Antibody Sampling [14]		√						√	√
Concomitant medication/treatment [15]	√								
Adverse events	√								

[1] Pregnancy test is required for women of childbearing potential and follicle stimulating hormone (FSH) is required if confirmation of postmenopausal status is needed.

[2] SARS-CoV-2 diagnostic test by polymerase chain reaction (PCR) or other commercial or public health assay: If a

subject has a positive test within the 14 days prior to study drug administration, an additional test at screening does not need to be performed. Tests during follow-up are requested, but if missed or done out of window, this will not be considered a protocol deviation.

[3] Radiographic lung imaging examination: Including lung CT or chest X-ray. If this procedure was performed as standard of care in the 14 days prior to study drug administration and radiographic infiltrates are present, this may be used, and imaging is not required at Screening or Day 1.

[4] Arterial blood gas analysis, finger blood oxygen saturation: arterial blood gas analysis: PH, partial pressure of oxygen, partial pressure of carbon dioxide, total carbon dioxide, oxygen saturation, actual bicarbonate, standard bicarbonate, base excess, anion gap. If the interval between arterial blood gas analysis performed during screening and dosing is less than 24 hours, a repeated test is not required on Day 1 predose. If Day 7 and/or 14 visits are conducted as outpatient visits, it is not necessary to perform an this procedure.

[5] Pulse oximetry should be recorded on a daily basis while the subject is hospitalized. The lowest registered level from each day should be recorded.

[6] Clinical status evaluation: 8-category ordinal scale score: 8, Death; 7, ventilation in addition to ECMO, CRRT or pressors; 6, Intubation and mechanical ventilation; 5, NIV or high-flow oxygen; 4, Hospitalization with oxygen by mask or nasal prongs; 3, Hospitalization without oxygen supplementation; 2, Limitation of activities, discharge from the hospital; and 1, No limitation of activities, discharge from hospital.

[7] ECG: Including but not limited to heart rate, QT, QTc, QTcF and P-R interval.

[8] Routine CBC: White blood cells, red blood cells, hemoglobin, hematocrit, mean cell volume, platelets, absolute neutrophil count and percentage, absolute lymphocyte count and percentage, absolute monocyte count and percentage, absolute eosinophil count and percentage, absolute basophil count and percentage. Blood biochemistry test: blood glucose; liver and kidney functions: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein , albumin, total bilirubin, direct bilirubin, alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), creatinine, blood urea nitrogen (BUN), uric acid; serum electrolytes: potassium, sodium, chlorine, calcium, magnesium, inorganic phosphorus. Coagulation function: prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), D-dimer. For screening, labs drawn before informed consent may be used if they are collected within 72 hours of study drug administration. Please see Section 6.2 for details.

[9] Dipstick is acceptable. Microscopic analyses if dipstick abnormal.

[10] Cytokines such as IL-1RA, IL-1β, IL-2, IL-6, IL-7, IL-10, GCSF, GM-CSF, CCL2, CCL3, CCL17, CXCL10, TNF-α and IFN-γ in serum.

[11] SOFA (Sequential Organ Failure Assessment score): see Appendix 3.

[12] Dosing: intravenous infusion. On Day 1, all corresponding assessments will be completed before dosing.

[13] Only applies to subjects in Part 2 randomized to the PK/ADA subgroup. Pharmacokinetic Samples will be collected on Day 1 predose, Day 1 end of infusion (±15 minutes), Day 7, Day 14, and Day 30. The Day 30 sample only must be collected if the subject is still hospitalized or is able to come in for an outpatient blood draw.

[14] Only applies to subjects in Part 2 randomized to the PK/ADA subgroup. The Day 30 sample only must be collected if the subject is still hospitalized or is able to come in for an outpatient blood draw.

[15] Recording concomitant medication/treatment: The concomitant medication mainly includes antiviral drugs, antibiotics, Glucocorticoid, and circulatory support drugs. Concomitant treatment mainly includes oxygen therapy, non-invasive/invasive mechanical ventilation, ECMO, and continuous renal replacement therapy (CRRT). Any SARS-CoV-2 vaccine history will be collected. For subjects who report they have received the SARS-CoV-2 vaccine, the following will be collected: Number of doses, date of dose(s) and brand name.

[16] If subject is discharged from the hospital during the study, complete an unscheduled SOFA score, ABG and PaO2/FiO2 ratio based on the last arterial blood gas analysis performed while the subject was hospitalized.

*If dosing occurs within 24 hours of screening, any Predose procedures done during screening do not need to be repeated. SOFA, troponin, clinical status assessment must be collected prior to dosing. Please see Section 6 for details.

**If subject is discharged prior to these visits, they may occur as outpatient or telephone visits. Please see Section 6 for details.

Abbreviations

ANC	Absolute neutrophil count
AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
ADCC	Antibody-dependent cell-mediated cytotoxicity
AB	Actual bicarbonate
AESI	Adverse Event of Special Interest, AESI
AG	Anion gap
AUC	Area Under the Curve
APTT	Activated partial thromboplastin time
ADA	Anti-Drug Antibody
AST	Aspartate aminotransferase
ALT	alanine aminotransferase
ALP	Alkaline phosphatase
CIA	Collagen-Induced Arthritis
CRP	C-Reactive Protein
CL	Clearance
CSF2	Colony-Stimulating Factor 2
CAR-T	Chimeric antigen receptor
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
C_{max}	Maximum concentration
CBC	Complete blood count
CFR	Code of Federal Regulations
CDC	complement dependent cytotoxicity
CRP	C-Reactive Protein
CT	Computed Tomography
COVID-19	Coronavirus Disease 2019
CRS	Cytokine Release Syndrome
CRRT	Continuous renal replacement therapy

CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CRO	Clinical Research Organization
COPD	Chronic obstructive pulmonary disease
DLT	Dose-Limiting Toxicity
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EOI	End of Infusion
EC	Ethic Committee
ECMO	Extracorporeal membrane oxygenation
FDA	Food and Drug Administration
FIH	First-in-human
FSH	Follicle Stimulating Hormone
GGT	Gamma-glutamyltransferase
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
HIV	Human Immunodeficiency Virus
HED	Human Equivalent Dose
ICH	International Committee on Harmonization
IDMC	Independent Data Monitoring Committee
IRR	Infusion Related Reaction
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
INR	International normalized ratio
JIA	Juvenile Idiopathic Arthritis
LAR	Legally Authorized Representative
LDH	Lactate Dehydrogenase
MAS	Macrophage Activation Syndrome

MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
MAD	Maximum Administered Dose
NIV	Non-Invasive Mechanical Ventilation
NCI	National Cancer Institute
NLR	Neutrophil to lymphocyte ratio
NYHA	New York Heart Association
NOAEL	No Observed Adverse Effect Level
PBMC	Peripheral Blood Mononuclear Cell
PAP	Pulmonary Alveolar Proteinosis
PD	Pharmacodynamics
PIP	Proximal Interphalangeal Joint
pSTAT5	Phosphorylated Signal transducer and activator of transcription 5
PK	Pharmacokinetics
PaO2	Partial Pressure of Oxygen
PT	Prothombin time
PCR	Polymerase chain reaction
Q1W	Once weekly
RTSM	Randomization and trial supply management
RBC	Red Blood Cell
SOFA	Sequential Organ Failure Assessment
SAE	Serious Adverse Event
SD	Standard Deviation
SARS-COV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SRC	Safety Review Committee
SaO2	Oxygen Saturation
SC	Subcutaneous
SAP	Statistical Analysis Plan
T_{max}	Time reach the peak concentration
$T_{1/2}$	Elimination half-life

TCR	Tissue-cross Reactivity
TK	Toxicokinetic
TCO2	Total Carbon Dioxide
TEAE	Treatment Emergent Adverse Event
TB	Tuberculosis
V_{ss}	Volume of Distribution at Steady State
V_z	Volume of distribution

1. Background

Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), also known as Colony-Stimulating Factor 2 (CSF2), is a member of the colony-stimulating factor family of hematopoietic growth factors. It was first known as an in vitro inducer for bone marrow progenitor cells to differentiate and proliferate into a single colony. GM-CSF is a monomeric glycoprotein cytokine, which may be produced by many cells including myeloid cells, dendritic cells, T cells, B cells, non-hematopoietic cells (such as endothelial cells, chondrocytes and alveolar epithelial cells) and even tumor cells (Avci et al., 2016). GM-CSF binds to heterodimeric receptors on bone marrow cells and neutrophils and activates GM-CSF receptors to initiate a variety of downstream signaling pathways, including Janus kinase signal transducer transcription- suppressor of cytokine signaling (JAKSTAT-SOCS), mitogen-activated protein kinase (MAPK), phosphatidylinositol 3 kinase (PI3K), and nuclear factor κB signaling pathway (NF-κB) (Hansen et al., 2008; Jenkins et al., 1998; Sato et al., 1993; Broughton et al., 2015; Hercus et al., 2017).

GM-CSF, as a key upstream trigger factor in the inflammatory cytokine cascade, can enhance the effects of neutrophils and macrophages, to increase the expression of adhesion molecules, produce inflammatory cytokines and activate the phagocytosis. In addition, GM-CSF is also an important cytokine that induces the polarization of monocytes to the inflammatory M1 phenotype and promotes the activation of macrophages, and the macrophages secrete a large number of inflammatory cytokines such as IL-6, TNF-α, etc., to involve in tissue inflammation (Hamilton, 1980).

Indeed, the strong proinflammatory effects of GM-CSF make it a prime target in acute inflammatory conditions where elevated GM-CSF has been implicated in orchestrating a cytokine storm. At least three such syndromes share immunological and pathologic features of a cytokine storm: chimeric antigen receptor (CAR)-T cell therapy related cytokine release syndrome (CRS) and neurotoxicity, macrophage activation syndrome (MAS) and most recently, acute respiratory distress syndrome (ARDS) in severe coronavirus disease (COVID-19) cases caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).

CAR-T therapy is revolutionizing cancer treatment, but its application is limited by life-threatening toxicities such as CRS and neurotoxicity (Gust, 2019) attributable to hyperactive T cells and monocytes/macrophages. It has been reported that GM-CSF neutralizing antibody during CAR-T therapy prevented CRS and neuroinflammation and both GM-CSF neutralization and GM-CSF knockout in CAR-T cells enhanced antitumor activities in a mouse ALL xenograft model (Figure 1, Sterner et al., 2019). In addition, GM-CSF inactivation in this setting abolished macrophage-dependent secretion of factors, including monocyte chemoattractant protein 1 (MCP-1), IL-6, and IL-8 (Sachdeva M, 2019). Compared to tocilizumab that has been widely used to treat cytokine storm caused by CAR-T cells, GM-CSF antibodies can achieve better treatment effect, especially in regulating the broad spectrum of cytokines and inhibiting neurotoxicity. Based on these findings, a clinical trial of GM-CSF antibody lenzilumab in CAR-T therapy is planned (Sterner et al., 2019).

Figure 1. GM-CSF antibodies inhibited the release of cytokines caused by CAR-T cells (Sterner et al., 2019).

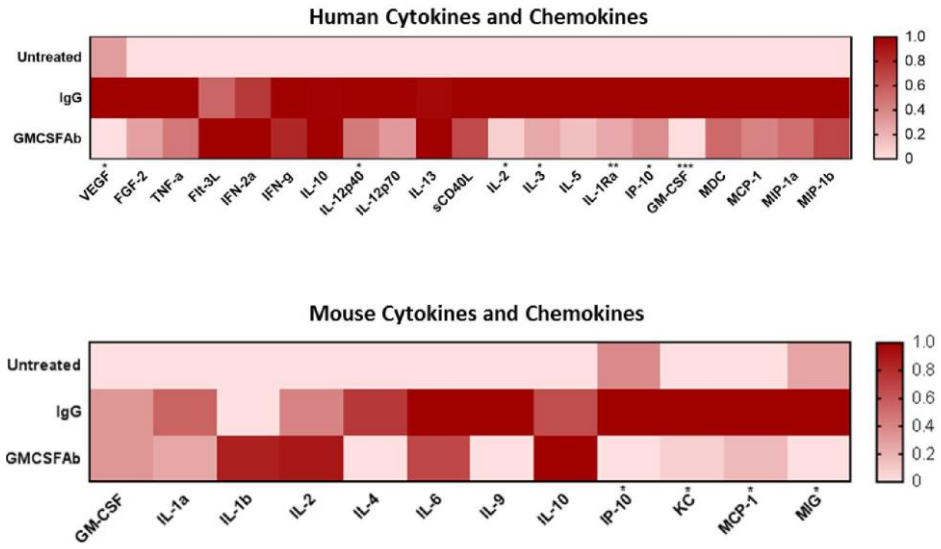
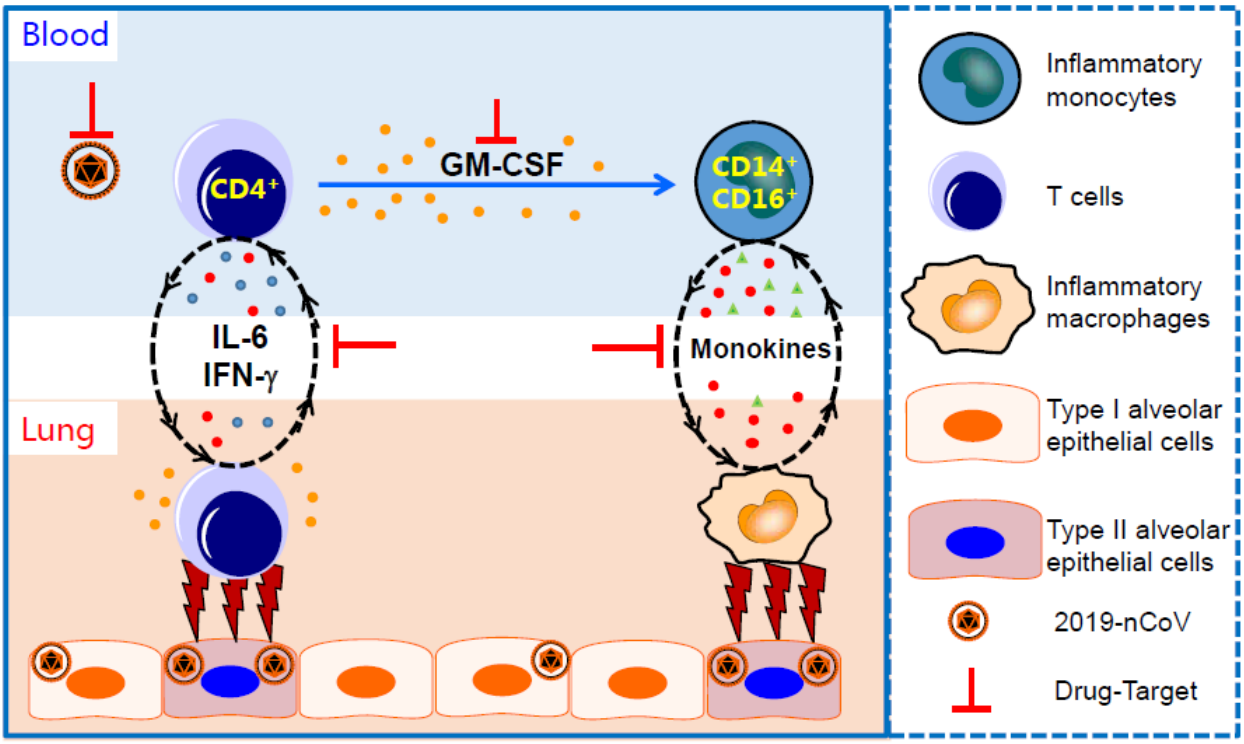


Figure 2. Infection of SARS-CoV-2 Caused Hyperactivation of T helper cells to Drive Aberrant Monocyte Activation



Both T cells and monocytes produce large amounts of cytokines and chemokines which feed forward on the immune cells to precipitate a cytokine storm and tissue damage ensues. GM-CSF neutralization could stop this cycle. (Figure 2 from Zhou Y, 2020; caption added).

In the recent COVID-19 epidemic caused by the coronavirus SARS-CoV-2 in China, 10-20% of the pneumonia patients developed severe or critical conditions that required intensive care. These

complications included ARDS, multiple organ failure and sometimes death. The clinical features (Huang, 2020) and immunopathology (Xu, 2020) of patients with COVID-19 in China have now been reported, and they remarkably resembled those found in SARS (Channappanavar, 2017). Common features among COVID-19 patients particularly those seriously or critically ill included lymphopenia and significantly higher than normal levels of inflammatory cytokines (IL-1, IL-7, IL-8, IL-9, IL-10, basic FGF, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1A, MIP-1B, PDGF, TNF-α, and VEGF) (Huang, 2020). Most studies also reported massive production of IL-6, CRP, D-dimer and ferritin – all consistent with cytokine storm (Wang, 2020). Importantly, lung pathology revealed heavy interstitial lymphocytic infiltrates along with diffuse alveolar damage with fibromyxoid exudates, multinucleated giant cells and hyaline membrane formation, indicative of ARDS (Xu, 2020). Interestingly, these pathological features and lung CT imaging characteristics are also remarkably similar to those reported for a subset of systemic Juvenile Idiopathic Arthritis (JIA) patients that developed MAS that led to severe immunopathology and lung disease (Schulert, 2019). Finally, peripheral blood mononuclear cell (PBMC) immunophenotyping showed an abundance of highly active GM-CSF-producing T helper cells and pathogenic monocytes in COVID-19 patients (Xu, 2020; Zhou, 2020).

It seems clear from these recent reports that severe COVID-19 bears all the hallmarks of a cytokine storm instigated by exuberant immune cells producing GM-CSF and IL-6. They drive aberrant monocyte and T cell activation which in turn produce more cytokines and chemokines in a feed forward cycle that culminates in profound tissue injury, airway constriction, vascular collapse and organ failure. Without intervention, the clinical course is expected to be dire for COVID-19 patients in severe or critical conditions. Currently, based on the experience of IL-6R antibody tocilizumab in managing CAR-T induced CRS, tocilizumab is being tested for reducing cytokine storm and its complications in a clinical trial of COVID-19 patients. Based on the analysis above and progress made in CAR-T therapy with the introduction of GM-CSF inhibition, GM-CSF neutralizing antibodies such as TJ003234 may prevent or curb cytokine storm and immunopathology in COVID-19 and consequently buy more time for viral clearance.

TJ003234 is a recombinant anti-GM-CSF humanized monoclonal antibody independently developed by I-Mab Biopharma Co., Ltd. At present, a number of preclinical studies have been conducted on TJ003234, demonstrating that TJ003234 is a specific and effective antagonist of human GM-CSF/GM-CSFR pathway. TJ003234 has shown significant inhibitory effect on GM-CSF mediating GM-CFSR signaling in vitro and in vivo. Blocking the biological activity of GM-CSF suppresses the activation of pro-inflammatory monocytes, leading to the potential clinical benefits to patients with cytokine storms.

In December 2018, the US Food and Drug Administration (FDA) approved the first study of TJ003234 for human use in healthy volunteers. The phase I study was expected to obtain safe tolerated doses and pharmacokinetic characteristics of TJ003234 in humans, and currently the study has been completed. In this first human study, a single dose of TJ003234 up to 10 mg/kg in healthy subjects was well tolerated. The maximum tolerated dose was not reached. The increased TJ003234 exposure (C_{max} and AUC) was roughly proportional to the increase in dose. The $T_{1/2}$ was about 3 weeks within the test dose range of 0.3mg/kg to 10mg/kg. The clearance rate of TJ003234 decreased with increasing dose. The volume of distribution decreased slightly with the increasing dose. In the subjects in 3 mg/kg and 10 mg/kg cohorts, TJ003234 inhibited

GM-CSF-stimulated pSTAT5 levels by more than 90% for up to 2 weeks in 4 hours after dosing (full clinical study report submitted to FDA in January 2020).

1.1. Preclinical Studies

For information on TJ003234 preclinical studies, refer to the Investigator's Brochure. It is summarized as follows.

1.1.1 Toxicological study

The toxicology studies of TJ003234 include toxicity pre-test in cynomolgus monkeys, toxicology and toxicokinetic tests in cynomolgus monkeys after being given TJ003234 by repeated intravenous injection for 4 weeks and recovery for 30 days, potential cross-reactions of TJ003234 to human and monkey tissues and in vitro hemolysis testing of TJ003234 in rabbit blood erythrocytes.

In the toxicity pre-test in cynomolgus monkeys, a control group and test groups (TJ003234 Solution for Injection at doses of 20.65, 61.95, 216.2 mg/kg respectively) were established. Animals were treated once a week for 3 consecutive weeks (3 times in total). No mortality occurred in the study, and all animals survived to the planned necropsy. No obvious TJ003234-related clinical symptoms, changes in body weights, food intake, and related hematological or coagulation parameters and clinical biochemical parameters were observed.

In a pivotal Good Laboratory Practice (GLP)-compliant toxicity study, 40 cynomolgus monkeys were randomly divided into 4 groups (5 animals/sex/group). On Days 1, 8, 15, 22, and 29 (4-week exposure), animals were administered by intravenous injection of the solvent control or test article (TJ003234 of 20, 60 or 200 mg/kg, 5 times in total). No Antidrug Antibody (ADA) formation was detected for all animals when the systemic exposure was reached, and no TJ003234-related deaths or morbidity occurred.

During a post-mortem recovery examination, a male animal had minimal congestion and multifocal alveolar protein in the lungs in the 20 mg/kg dose group. The alveolar protein was characterized by eosinophilic fibers and fluids in the alveoli, with a minimal increase in the number of alveolar macrophages with normal morphology. The animal's lung tissues showed negative by oil red O and PAS staining. Lung tissue SP-A and SP-D showed no interalveolar staining, and SP-B showed slight staining in a small number of alveoli, which was considered non-specific and believed not to be related to PAP (pulmonary alveolar proteinosis). This animal was normal by clinical observation and had normal respiratory functions throughout this study. The lung changes in male monkey were acute in nature and were considered to be caused by stress before or during euthanasia. Similar changes were not observed at higher dose levels or final necropsy. These data suggested that the animal's alveolar staining was not related to PAP.

During the terminal necropsy, a male animal in the 200 mg/kg group was found to have focal neuronal degeneration, edema, and a glial scar under microscopy. Given the low incidence of this change, these lesions were likely to be incidental and were not related to the test substance. During the terminal necropsy, a male animal in the 200 mg/kg group was found to have pulmonary granulomas, and the gross observations showed multifocal yellowing of the lung's head lobe, middle lobe and caudate lobe and yellow lumps near the lung hilus. Since oil red O and PAS stains showed negative and SP-A, SP-B and SP-D in the alveoli were not specifically

stained, the animal's lung findings were not much related to the PAP. Although these lung changes occasionally occurred in background lesions of non-human primates, the effect of the test substance on the immune system that may affect the original lesions could not be completely ruled out.

Based on the above results, the No-Observed-Adverse-Effect Level (NOAEL) dose of TJ003234 in cynomolgus monkeys was 60 mg/kg.

1.1.1.1 Tissue-cross Reactivity in Human and Cynomolgus Monkey

In this GLP-complaint tissue-cross reactivity (TCR) study, Biotin-TJ003234 (2.5, 5 and 10 μg/mL), with cryo-sections from histologically normal frozen human and cynomolgus monkey tissues (panels of 40 tissues for human and cynomolgus monkey; 3 donors/panel) was assessed in this study. All tissues were validated by staining method. The positive control of the study was GM-CSF protein.

Specific positive staining was observed with biotin-TJ003234 in secretory cells within tissues of the gastrointestinal tract in the human and cynomolgus money tissues panels examined. Additional specific positive staining was observed with biotin-TJ003234 in epithelial cells in cynomolgus monkey lung and parotid. The specific positive staining observed is consistent with GM-CSF expression, no tissue cross-reactivity was observed.

1.1.1.2 In vitro Hemolysis Assay

In this GLP-complaint hemolysis study, approximately 15 mL of blood was collected from a male New Zealand white rabbit via a jugular vein. Red blood cells (RBC) were suspended in 0.9% sodium chloride injection solution to a final concentration of 2%. The hemolytic potential of TJ003234 at concentration of 105.5 mg/mL was tested. After TJ003234 was added to the samples, the tubes were placed into a water bath set at 37 ℃± 0.5 ℃for 3 hours and observed once every 15 minutes during the first hour and every hour during the last two hours for hemolytic potential.

There was no hemolysis noted in RBC incubated with TJ003234 (105.5 mg/mL). There was also no RBC coagulation noted. TJ003234 at concentration of 105.5 mg/mL had no hemolytic potential.

1.1.1.3 Immunotoxicity and immunogenicity

The immunotoxicity study was carried out together with the 4-week toxicology study in cynomolgus monkeys. The cytokines are one of important immune function parameters. No changes in cytokines were found after intravenous injection of TJ003234. The concentration and change of cytokine levels at all time points during the dosing period on Day 1 and Day 22 in the TJ003234 group were similar to those in the control group, and the values were within the historical variation range, without any toxicological significance. In addition, TJ003234 specifically bound and neutralized the secreted cytokine GM-CSF, which was not a cell target. Therefore, TJ003234 was expected to have a very low risk of inducing cytokine release

syndrome in human bodies, so human whole blood or PBMCs was not used for cytokine release analysis. All samples were negative for anti-drug antibodies during the dosing and recovery periods; therefore, no anti-drug antibody (ADA) formation was detected, which proved that TJ003234 had low preclinical immunogenicity.

1.1.2 Pharmacological Studies

Pharmacological studies included in vitro and in vivo pharmacological studies. Studies have shown that TJ003234 can block the GM-CSF/GM-CSFR interaction, prevent GM-CSFR-induced signaling pathways, and thereby neutralize the biological activity of GM-CSF. By inhibiting the functions of macrophages, TJ003234 can reduce the autoimmune responses. TJ003234 did not show antibody-dependent cell-mediated cytotoxicity (ADCC) effect on human monocytes and complement dependent cytotoxicity (CDC) effect on human PBMC. The evaluation of the effects of TJ003234 on the in vitro monocyte activation to mimic the viral RNA stimulation demonstrated that TJ003234 treatment could suppress the activation of as well as cytokine production by proinflammatory monocytes.

1.1.2.1 In vitro Pharmacology

As shown in Table 2, TJ003234 was characterized through a series of in vitro studies to describe 1) cross reactivity with GM-CSF from various species; 2) binding specificity to human GM-CSF over its structurally and functionally close related proteins; 3) ability to block the interaction of GM-CSF with GM-CSF receptor (CD116 or GM-CSFR); 4) ability to inhibit GM-CSF mediated STAT5 phosphorylation in PBMCs and whole blood; 5) binding profiles to FcRn, Fcγ receptors and C1q; 6) ADCC and CDC study; 7) inhibition of in vitro monocyte activation which is used to mimic the COVID-19 viral RNA stimulation of primary monocytes.

Table 2. Results of in vitro pharmacological studies

Test Item	Test System	Test Results
Cross-reactivity of TJ003234 against different species of antigens	ELISA	The EC50s of TJ003234 against human and monkey GM-CSF antigens were 13.22 ng/mL and 8.44 ng/mL, respectively, with similar binding effect. TJ003234 did not bind to mouse and rat GM-CSF antigens.
Antibody specificity of TJ003234	ELISA	TJ003234 could bind human or monkey GM-CSF, with EC50 of 6.435-6.722 ng/mL and 6.536 ng/mL, respectively. TJ003234 could not bind to human G-CSF, M-CSF, IL-3 or IL-5.
Antibody receptor ligand blocking detection of TJ003234	ELISA	Two independent tests showed that the half-maximum blocking concentrations (IC50) of TJ003234 block the binding of human GM-CSF to its receptor CD116 were 112.4 ng/mL and 122.1 ng/mL, respectively, indicating that TJ003234 could effectively block the binding of human GM-CSF to CD116.
Effect of TJ003234 on GM-CSF-mediated	FACS	TJ003234 could effectively block STAT5 phosphorylation in recombinant human-derived or

Test Item	Test System	Test Results
STAT5 phosphorylation signals		cynomolgus monkey GM-CSF-mediated PBMCs. The IC50 of its inhibition of human-derived GM-CSF-mediated STAT5 phosphorylation was 0.34-1.70 ng/mL, and its IC90 was 4.15-12.76 ng/mL. The IC50 of its inhibition of cynomolgus monkey GM-CSF-mediated STAT5 phosphorylation was 0.11-4.54 ng/mL, an its IC90 was 0.62-22.07 ng/mL.
Roles of TJ003234 on STAT5 phosphorylation induced by GM-CSF activation in human whole blood	FACS	Antibodies could neutralize the activation of the GM-CSF-induced STAT5 phosphorylation pathway in a dose-dependent manner. IC50s of donors 1, 2 and 3 were 0.35 μg/mL, 1.81 μg/mL, 0.44 μg/mL, respectively; and the IC90 of donors 1, 2 and 3 were 3.18 μg/mL, 4.67 μg/mL, 1.55 μg/mL, respectively.
Affinity of TJ003234 antibody to human GM-CSF antigen	Biacore	The three batches of antibodies had strong affinity to the human antigen GM-CSF, and there was no significant difference between the three batches of antibodies.
ADCC and CDC Effects of TJ003234	ELISA	TJ003234 did not show antibody-dependent cell-mediated cytotoxicity (ADCC) effect on human monocytes and complement dependent cytotoxicity (CDC) effect on human PBMC.
Binding affinity of TJ003234 antibody to FcRn, Fcγ receptor and C1q	Biacore	The affinity between the antibody and each Fc receptor and complement C1qB was as follows (in descending order): CD64, C1qB, CD16a (176Val), CD16a (176Phe), FcRn, CD32a, CD16b, CD32b. IgG1 had a high affinity to CD64, but had a relatively low affinity to CD32. The above test results were consistent with the typical characteristics of IgG1, and there was no significant difference between the three batches of antibodies.
Inhibition of in vitro monocyte activation by TJ003234	Luminex	TJ003234 treatment significantly decreased the production of proinflammatory cytokines and chemokines by activated monocytes including IL-5, IL-7, IL-9, IL-10, IL-12p70, IL-13, IL-15, IL-17A, bFGF and Eotaxin.

1.1.2.2 In vivo Pharmacology

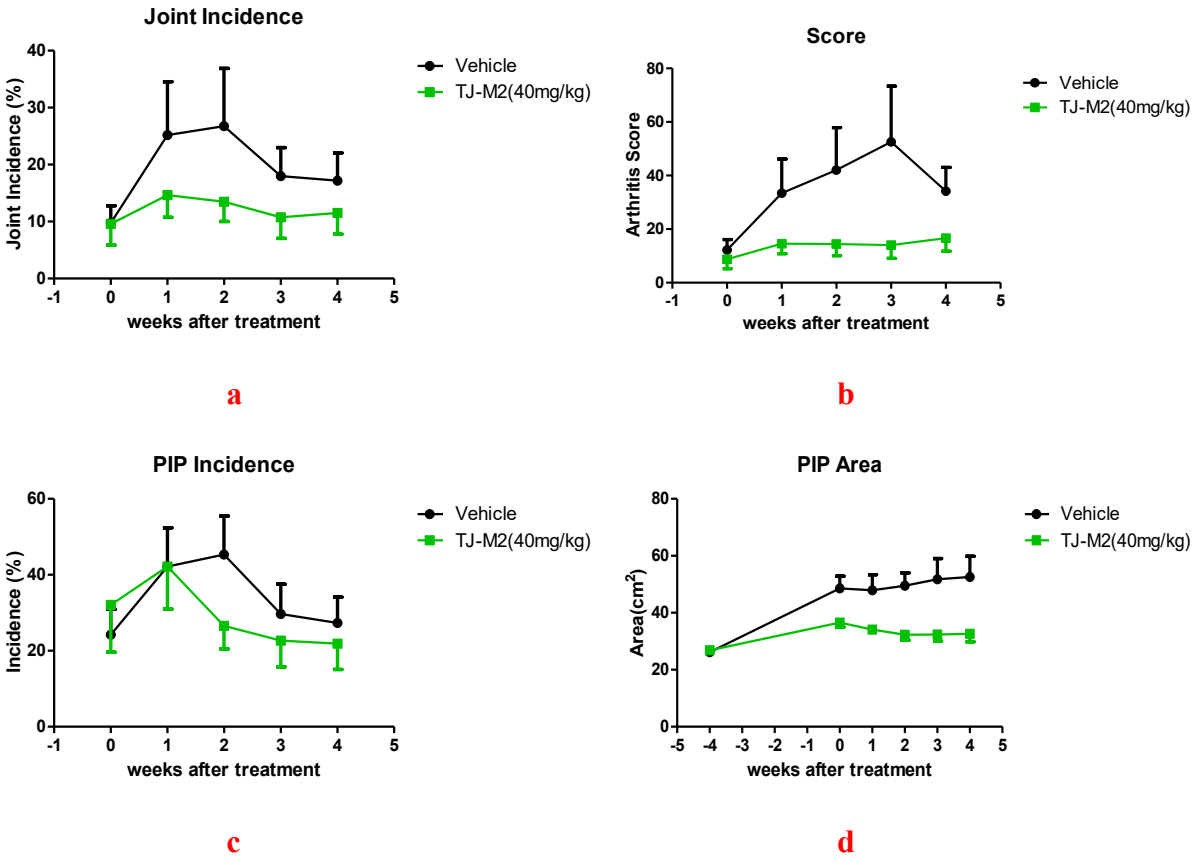
1.1.2.2.1 In vivo Efficacy of Repeat Dose TJ003234 on Type II Collagen Induced Arthritis (CIA) Model in Cynomolgus Monkeys

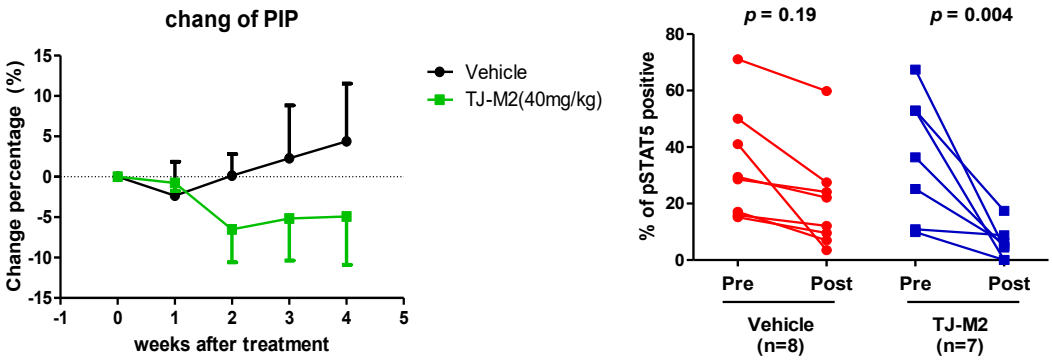
The in vivo therapeutic efficacy of TJ003234 for type II collagen induced arthritis was evaluated in cynomolgus monkeys with overt arthritic symptoms. Seventeen female cynomolgus monkeys were randomly assigned to 3 groups and received either no immunization and no administration

(n=1), or immunization and vehicle (n=8) or test article (n=8, TJ003234 at 40 mg/kg).

Animals that developed arthritis were randomly assigned to 2 groups (8F/group) and administered vehicle or 40 mg/kg TJ003234 by intravenous (IV) injection once a week for 4 doses. Arthritis severity was quantified by joint incidence (# of inflamed joints over the total # of joints analyzed) and arthritis score. Proximal interphalangeal (PIP) area was also applied to quantify joint swelling of arthritis. Additionally, phosphorylation of STAT5 downstream of GM-CSFR activation was used as a proximal pharmacodynamic (PD) marker reflecting the TJ003234 mediated blockade of GM-CSF signaling, and was evaluated using PBMCs isolated from monkeys before or 24 hours after TJ003234 administration by FACS.

Figure 3. In vivo Efficacy of Repeat Dose TJ003234 on Type II Collagen Induced Arthritis (CIA) Model in Cynomolgus Monkeys





e f

Comments: Joint incidence (a), arthritis score (b), PIP incidence (c), PIP Area (d), PIP area change percentage (e) and % of pSTAT5 positive cells in PBMCs (f) in CIA monkey model

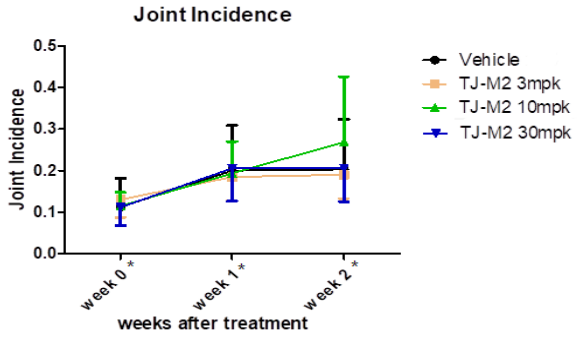
As shown in Figure 3, the treatment at 40 mg/kg of TJ003234 could significantly reduce the severity of CIA, indicating that TJ003234 is effective in treating CIA in this model.

1.1.2.2.2 Dose response relationship of TJ003234 in monkey CIA Model

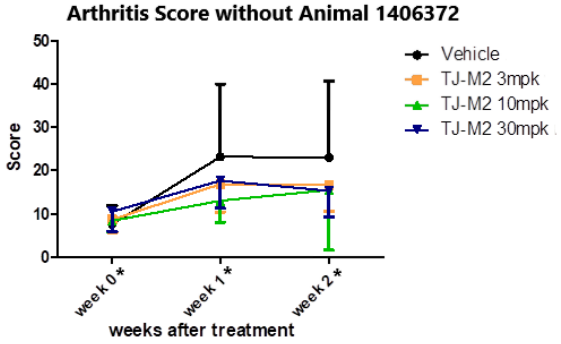
Using the same CIA monkey model, a dose-response study was conducted to establish the PK/PD relationship of TJ003234. Twenty-eight female cynomolgus monkeys were randomly assigned to 4 groups and received immunization and 0, 3, 10 and 30 mg/kg TJ003234 once via IV injection.

Similar clinical endpoints (joint incidence, arthritis score, PIP incidence, PIP Area, PIP area change percentage) and proximal PD marker (phosphorylation of STAT5) were used in this study to evaluate the in vivo efficacy. As shown in Figure 4. Dose response relationship of TJ003234 in monkey CIA Model, the joint incidence was not affected by treatment with TJ003234; the mean arthritis scores were progressed in a decreased fashion after the TJ003234 treatment in all test groups compared to control group, yet no dose-response was found; no consistent difference in PIP incidence and PIP area between vehicle control and TJ003234 treatment; the treatment at 30 mg/kg of TJ003234 significantly reduced the PIP area in week 2 compared with week 1; treatment with TJ003234 (3, 10, or and 30 mg/kg once via IV injection) reduced pSTAT5 levels when compared to the vehicle control group.

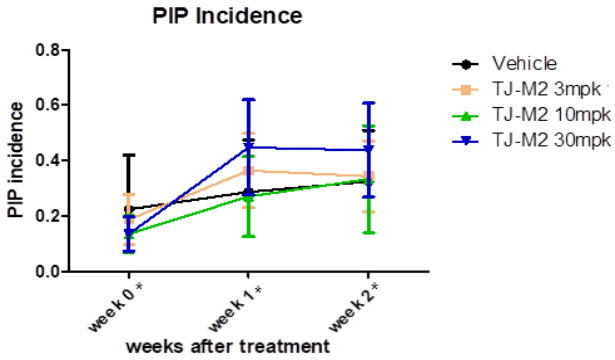
Figure 4. Dose response relationship of TJ003234 in monkey CIA Model



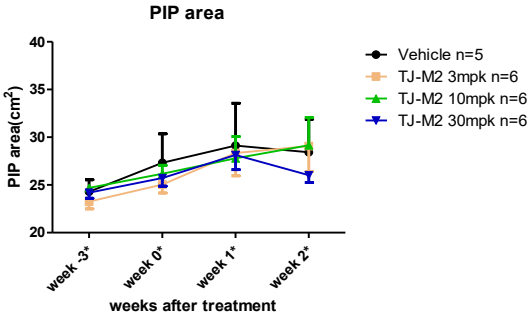
a



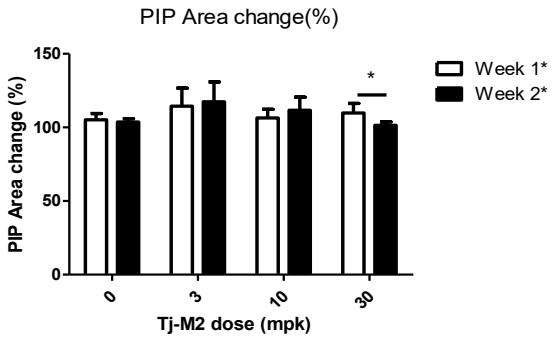
b



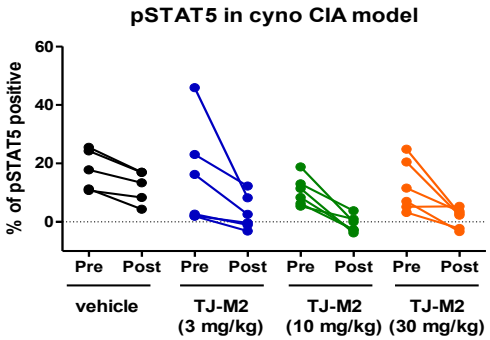
c



d



e



f

Comments: Joint incidence (a), arthritis score (b), PIP incidence (c), PIP Area (d), PIP area change percentage (e) and % of pSTAT5 positive cells in PBMCs (f) following 0, 3, 10, 30 TJ003234 single IV injection in CIA monkey model

A systematic exposure study was conducted for all animals. After a single intravenous injection of TJ003234 into CIA model monkeys, the mean peak concentrations (C_{max}) at 3, 10, and 30 mg/kg were 76.137, 236.313, and 572.236 μg/mL, respectively; the mean areas under concentration-time curve were 2143.691, 9361.553, and 14134.021 μg • hr/mL, respectively. Based on the mean C_{max} and AUC_{last}, TJ003234 exposure rose with proportionally increased dose levels from 3 mg/kg to 30 mg/kg.

In summary, a single dose of TJ003234 within the range of 3 to 30 mg/kg can inhibit the development of arthritis symptoms without exhibiting a significant dose-dependence: the systemic exposures (Cmax and AUC) within the dose range increase proportionally with the dose.

1.1.3 Pharmacokinetic study

1.1.3.1 Single-dose Pharmacokinetics

Based on the cross-reaction of TJ003234 with cynomolgus GM-CSF antigen and no affinity with rodent GM-CSF antigen and the fact that TJ003234 can block the GM-CSF-mediated STATS5 phosphorylation signals in the cynomolgus monkey-derived PBMCs, cynomolgus monkeys were selected as the sole animal species. In a single-dose pharmacokinetic study, cynomolgus monkeys (3 animals/sex/group) were given 5, 25, and 50 mg/kg of TJ003234 by intravenous injection respectively. No sex-specific difference in systemic exposure were observed, and C_{max} and $AUC_{0\text{-last}}$ increased proportionally in the last dose with the range of 5-50 mg/kg. The C_{max}/dose and $AUC_{0\text{-last}}$/dose in all dose groups were similar within the dose range of 5.0 mg/kg to 50 mg/kg, indicating that TJ003234 met the linear pharmacokinetic behaviors within the dose range. With the entire dose levels, the mean elimination half-life ($T_{1/2}$) ranged from 9.0 to 10.0 days, the clearance (CL) ranged from 0.332 to 0.406 mL/h/kg, the apparent volume of distribution (V_z) ranged from 114 to 126 mL/kg, C_{max} was 112-1220μg/mL and $AUC_{0\text{-last}}$ was 14800-124000 μg · h/mL.

The bioavailability of TJ003234 following subcutaneous injection was studied in cynomolgus monkeys following a single intravenous injection at 5 mg/kg and a single subcutaneous injection at 5 mg/kg, 25 mg/kg and 50 mg/kg, respectively. A linear subcutaneous pharmacokinetic profile was observed across three subcutaneous (SC) dose levels, with bioavailability of 77.4%, 78.8%, 72.6%, respectively. The rate of elimination was similar following IV and SC routes, indicating elimination of TJ003234 was independent of the route of administration in cynomolgus monkeys. No ADA was detected throughout the study.

1.1.3.2 Repeat-dose Pharmacokinetics

The toxicokinetic (TK) profile of TJ003234 across repeated IV doses were determined in conjunction with a GLP-compliant repeat-dose toxicology study in cynomolgus monkeys. In this study, 40 cynomolgus monkeys were randomly assigned into 4 groups (5/sex/group) and administered TJ003234 at 0, 20, 60 or 200 mg/kg via IV injection once weekly (Q1W) for a total of 5 doses.

No significant gender differences in systemic exposure (C_{max} and $AUC_{0\text{-t}}$) following the 1st and 4th doses were observed. The systemic exposure increased dose proportionally after the 1st dose from 20 to 200 mg/kg. There were no significant differences in the concentration-time curves among individual animals within each dose level. Following the 4th dose, toxicokinetic parameters, including time of maximum concentration (T_{max}), C_{max}, $AUC_{0\text{-t}}$, and clearance (CL) were similar to those following the first dose. Exposure did not decrease significantly following the 4th dose when compared to the 1st dose, indicating the absence of an increased clearance due to potential neutralizing ADA formation. The immunogenicity results confirmed that all samples

were detected as anti-TJ003234 antibody negative in the dosing phase. Mild accumulation was noticed in AUC_{0-t} and C_{max} at all dose levels: for the 4th vs 1st dose, the ratio of C_{max} was 1.27, 1.29, 1.15, and the ratio of AUC_{0-t} was 1.49, 1.41, 1.35, for 20, 60, 200 mg/kg dose levels, respectively.

1.2. Clinical Study

The US FDA approved the Investigational New Drug (IND) of TJ003234 in healthy volunteers in December 2018. The phase I trial was designed as a single-center, randomized, double-blind, placebo-controlled, single-dose escalation study.

The study objectives were to evaluate safety, tolerability, PK, PD, and immunogenicity of TJ003234 following a single dose. This study enrolled 32 healthy subjects at the dose levels of 0.3 mg/kg, 1 mg/kg, 3 mg/kg and 10 mg/kg. Eight subjects were randomized at a ratio of 3:1 in each dose cohort to receive either TJ003234 or placebo. In the first cohort, to mitigate any unforeseen safety issues, the first 4 of the 8 subjects were individually dosed at intervals that were, by protocol, at least 24 hours apart. In each study cohort, subjects were screened within 27 days prior to admission to the site. Subjects were admitted to the site on the day prior to dosing (Day -1) for pre-dose study procedures and randomization. On dosing day (Day 1), a single dose of TJ003234 was administered IV over a maximum 2-hour period. Subjects were observed overnight. On Day 2, after completion of the study procedures and assessments, subjects were discharged from the site. The 7-day dose-limiting toxicity (DLT) observational period started at the completion of dosing (end of infusion [EOI]). The study period was defined as the time of dosing through the end of the study (a duration of 90 days). Subjects returned to the site for outpatient visits on Days 3, 5, 8 (week 1), 15 (week 2), 29 (week 4), 43 (week 6), 57 (week 8), 71 (week 10) and 90 (week 13). Day 90 was considered the end of study (EOS) visit.

Dose escalation occurred sequentially after review of safety data for each dosing cohort by the safety review committee (SRC). Dose escalation to the next dose level proceeded uninterrupted as long as no pre-defined DLT or stopping criteria were met. According to the protocol, if the maximum tolerated dose (MTD) was not reached during dose escalation, the maximum administered dose (MAD) was defined as 10 mg/kg.

As of January 2020, the study has been completed and a clinical study report has been issued. Thirty-two (32) subjects enrolled into and completed TJ003234RAR101. There were no interruptions in dosing or early withdrawals. The Safety, PK, and PD Populations each include all 32 subjects. All treatment groups included both males and females as well as both black (43.8%) and white subjects (43.8%). There were no observable differences between the treatment groups that were anticipated to affect assessment of outcome. All major protocol deviations were reviewed by the medical monitor and determined to have no medical impact on the study.

Safety Results:

TJ003234 is well tolerated following a single IV dose up to 10 mg/kg in healthy subjects with

no maximum tolerated dose reached. The majority of adverse events (AEs) were mild to moderate. No serious adverse events were reported during the study. Overall, 8 of the 24 subjects who received TJ003234 and 3 of the 8 subjects who were on placebo reported treatment-related treatment-emergent adverse events (TEAEs). The most common AEs experienced by subjects dosed with TJ003234 were headache (25%, grade 1/2) and protein urine (25%, grade 1). These AEs were also the most common AEs reported by subjects received placebo (37.5%, grade 1/2 and 37.5%, grade 1, respectively). Two pulmonary AEs (Grade 1 cough and shortness of breath) were reported in one subject at Cohort 3 and were considered to be drug related. Two subjects from Cohort 1 and one subject from the Cohort 2 reported more than 20% decrease in FEV1 or FVC but the values were still within normal ranges, the changes were not observed in higher dose level cohorts. No clinically meaningful changes were observed in the dyspnea score.

Pharmacokinetic Results:

A summary of TJ003234 PK parameters following a single ascending dose of 0.3 to 10-mg/kg of TJ003234 administered to healthy subjects is presented below.

Table 3. TJ003234RAR101: TJ003234 Serum Pharmacokinetic Parameters following Single Ascending Intravenous Dose of TJ003234 in Healthy Subjects (PK Population)

Dose level	**C_{max}** (μg/mL)	**T_{max}** (h)	**AUC_{last}** (day*μg/mL)	**$AUC_{0-\infty}$** (day*μg/mL)	**$t_{1/2}$** (day)	**CL** (mL/day)	**V_{ss}** (L)	**V_z** (L)
0.3 mg/kg(n=6)	5.24 (56.2)	1.26 (1.00, 1.38)	80.3 (63.0)	85.7 (66.0)	22.5 (5.91)	290 (68.2)	8.26 (54.8)	9.15 (62.5)
1 mg/kg(n=6)	24.7 (19.4)	1.29 (1.27, 1.30)	289 (25.2)	298* (30.1)	20.5* (4.96)	258* (39.4)	5.71 (34.0)	7.41* (17.9)
3 mg/kg(n=6)	71.7 (10.3)	1.70 (1.70, 48.6)	1100 (27.1)	1250* (22.3)	20.1* (3.20)	200* (12.9)	5.26 (4.76)	5.75* (5.60)
10 mg/kg(n=6)	258 (13.6)	3.58 (1.77, 25.2)	3680 (27.2)	3860 (29.9)	20.6 (3.49)	178 (37.1)	4.63 (20.7)	5.23 (20.9)

C_{max}, AUC_{last}, $AUC_{0-\infty}$,, CL, V_{ss}, and Vz are presented as geometric mean (%CV). $t_{1/2}$ is presented as mean (SD). T_{max} is presented as median (min, max).

*At the 1 mg/kg and 3 mg/kg dose levels, the sample size reported for $AUC_{0-\infty}$, $t_{1/2}$, CL, and Vz is 5 subjects not 6 because each had too much variability in their concentration-time data and thus too low an r^2 to be acceptable for using the data in calculating these parameters.

Pharmacodynamic Results:

Four hours after dosing, the induction of pSTAT5 by ex vivo GM-CSF stimulation in the monocyte population was inhibited by at least 70% compared to the placebo following a single dose of TJ003234 for all dose groups. The induction of pSTAT5 by GM-CSF stimulation was inhibited by 94.1% at 4h postdose and 92.6% at 336h postdose following a single dose of 3mg/kg TJ003234. A comparable inhibitory effect was observed at 10mg/kg cohort, i.e. 95.3% inhibition

at 4hour postdose and 91.7% at 336 hour postdose. The inhibition was sustained for 2 weeks at 3 mg/kg and 10 mg/kg cohorts, suggesting the saturation of the pSTAT5 inhibition by the treatment at a 3 mg/kg dose and above.

Immunogenicity Results:

Two subjects in the 3 mg/kg TJ003234 cohort and one placebo subject were positive for ADA. The placebo subject was positive on Day 57 but negative on Day 90. One subject in the 3 mg/kg TJ003234 cohort developed a positive response at the Day 57 timepoint and maintained it when tested on Day 90. The other subject in the 3 mg/kg TJ003234 cohort was positive only on Day 90. No subject in the 10 mg/kg dose level was positive for ADA.

1.3. Benefits and Risks Assessment

1.3.1 Benefits

Based on the anti-inflammatory action mechanism of GM-CSF antibody, preclinical study results of TJ003234 and inhibition of in vitro monocyte activation by TJ003234, we believe that TJ003234 has potential benefits for the treatment of severe COVID-19.

1.3.2 Risks

Based on the results of preclinical studies conducted by I-Mab Biopharma and with reference to the published data in clinical studies of antibody with same/similar mechanism, the important potential risks of TJ003234 include:

- Pulmonary alveolar proteinosis
- Infections
- Infusion-related reactions

Pulmonary alveolar proteinosis (PAP)

GM-CSF promotes alveolar macrophage proliferation, which plays a critical role in lung defenses and surfactant homeostasis through catabolism of surfactant lipids and proteins. Autoantibodies against GM-CSF have been associated with the development of idiopathic autoimmune PAP, in which abnormal accumulation of pulmonary surfactant protein occurs within the alveoli due to insufficient clearance by GM-CSF-starved macrophages. Due to this association, there is a theoretical risk of developing PAP when long-term using therapeutic antibodies that target GM-CSF. No PAP has been indicated in TJ003234 non-clinical studies and the completed TJ003234 first-in-human (FIH) study (TJ003234RAR101). No clinically significant findings were identified in terms of pulmonary function tests and respiratory related signs/symptoms in this FIH study.

Infections

Due to the biological mechanism of TJ003234, blocking the GM-CSF may inhibit the functions

of macrophage and neutrophils, thus potentially may lead to risk of infections, especially long-term using. No infections were reported from TJ003234 animal studies. In the completed TJ003234 study in healthy adults, 24 adults received TJ003234, there was one adult experienced nasopharyngitis, and one adult experienced vulvovaginal mycotic infection. One of 8 adults who received placebo developed otitis media.

Infusion related reactions (IRR)

All therapeutic monoclonal antibodies used for oncology and immunologic therapies have the potential to cause infusion related reactions (IRRs). Symptoms vary with a wide spectrum of severity, ranging from mild fever and chills to life-threatening anaphylaxis with bronchospasm, and hypotension. Typically, IRRs to monoclonal antibodies develop within 30-120 minutes after the initiation of drug infusion, although symptoms may not show up until 24 hours. Most common symptoms of IRRs are fever, chills, nausea, vomiting, diarrhea, itching, flushing, rash, changes in blood pressure and heart rate, dyspnea, chest discomfort, back and abdominal pain. The risk of IRR declines with each subsequent course of therapy. Although premedication can help to prevent and/or reduce the severity of infusion reactions, anaphylaxis generally cannot be prevented by premedication. No IRR was identified in TJ003234 previous completed FIH study.

2. Objectives and Endpoints

2.1. Objectives

2.1.1. Primary Objective

To evaluate the efficacy and safety of TJ003234 in subjects with severe novel Coronavirus pneumonia (COVID-19) with supportive care.

2.1.2. Secondary Objectives

- To evaluate the effects of TJ003234 on cytokines in subjects with severe COVID-19.
- To assess the pharmacokinetics (PK) and immunogenicity potential of TJ003234 when administered as a single dose IV infusion in subjects with severe COVID-19.

2.2. Endpoints

2.2.1. Primary Efficacy Endpoint

Proportion (%) of subjects who are alive and free of mechanical ventilation at Day 30 among subjects who are non-mechanical ventilated at baseline.

2.2.2. Secondary Efficacy Endpoints

Key Secondary Efficacy Endpoints:

- Proportion (%) of subjects recovered by Day 14. Recovery is defined as the subject scoring a 3, 2, or 1 on the 8-category ordinal scale as defined below by Day 14 and subsequently does not progress to a score ≥ 4 for the remainder of the study. If a subject scores 3 at baseline, this subject is considered to be recovered if this subject's score improves to 1

or 2 by Day 14.

8, death; 7, ventilation in addition to extracorporeal membrane oxygen (ECMO), continuous renal replacement therapy (CRRT) or pressors; 6, intubation and mechanical ventilation; 5, non-invasive mechanical ventilation (NIV) or high-flow oxygen; 4, hospitalization with oxygen by mask or nasal prongs; 3, hospitalization without oxygen supplementation; 2, limitation of activities, discharge from hospital; and 1, no limitation of activities, discharge from hospital.

- Proportion (%) of subjects recovered by Day 30. Sustained recovery is defined as the subject scoring a 3, 2, or 1 on the 8-category ordinal scale as defined in the key secondary endpoint by Day 30 and subsequently does not progress to a score ≥ 4 for the remainder of the study. If a subject scores 3 at baseline, this subject is considered to be recovered if this subject's score improves to 1 or 2 by Day 30.

- All-cause mortality rate on Day 30.

Other Secondary Efficacy Endpoints:

- Time to sustained recovery among subjects alive by Day 30 [Time Frame: Day 1 through Day 30]: Day of sustained recovery is defined as the first day on which the recovered subject scores 3, 2 or 1 and maintains such score through Day 30 from the 8-category ordinal scale as defined in the key secondary endpoint. If a subject is scored at 3 at baseline, day of recovery is defined as the day on which this subject's score improves to 1 or 2 and maintains such score through Day 30.

- Length of hospitalization.

2.2.3. Exploratory Efficacy Endpoints

- Improvement in clinical status (Day 7, Day 14 and Day 30)
- Sequential Organ Failure Assessment score (SOFA score) (Day 7 and Day 14 from the day of dosing)
- Change from baseline in PaO2/ FiO2 (Day 7 and Day 14 from the day of dosing)
- Length of time to normalization of oxygen saturation which is defined as SpO2≥94% sustained minimum 24 hours
- Percentage of subjects requiring mechanical ventilation at Day 7 and Day 14 from the day of dosing.
- Change from baseline in serum cytokines, e.g. IL-1RA, IL-1β, IL-2, IL-6, IL-7, IL-10, GCSF, GM-CSF, CCL2, CCL3, CCL17, CXCL10, TNF-α and IFN-γ, etc. (Day 2, Day 3, Day 5, Day 7, and Day 14 from the day of dosing)
- Change from baseline in D-dimer, cardiac troponin, LDH, and ferritin levels (Day 7 and Day 14 from the day of dosing)
- Peripheral blood neutrophils-to-lymphocyte ratio (NLR)

2.2.4. Safety Endpoints

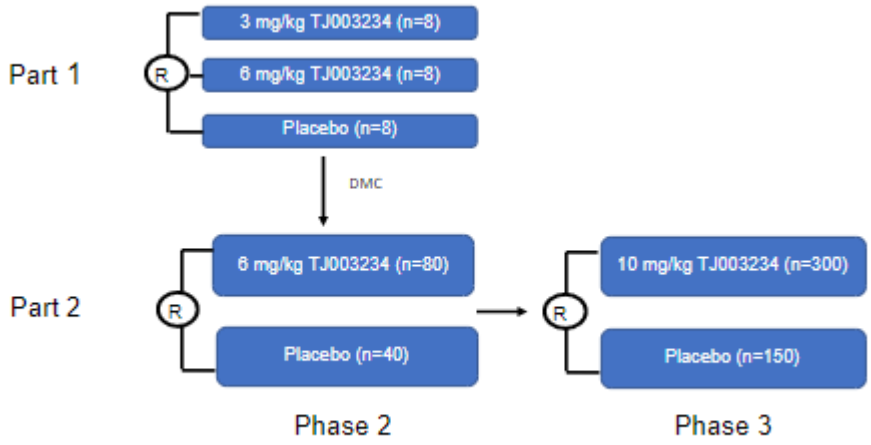
- Treatment-emergent Adverse events evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Criteria (CTCAE) (version 5.0),
- Changes from baseline in clinical laboratory parameters, physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), and radiographic lung imaging.

3. Investigational Plan

3.1. Study Design

This trial is designed as a two-part study to evaluate the efficacy and safety of TJ003234 administered by an IV infusion in subjects with severe COVID-19 with supportive care, and to assess the effect of cytokine elevations on the disease as well as the effect of TJ003234 on the levels of cytokines.

Figure 5: Study Design Schema



3.1.1. Part 1

Part 1 is designed as a randomized, double-blind, placebo-controlled, 3-arm, parallel-group study to evaluate the safety of TJ003234 in subjects with severe COVID-19. Potential subjects will be screened to assess their eligibility to enter the study within 3 days prior to study drug administration. A total of 24 eligible subjects will be randomized at a ratio of 1:1:1 to receive either a single dose of 3 mg/kg TJ003234, a single dose of 6 mg/kg TJ00324 or placebo, administered by IV infusion. Before and after the treatment, all subjects will be allowed to receive supportive care and/or additional treatments for COVID-19 and its complications per the Investigator. Up to twenty-four subjects will be enrolled in Part 1. If no more than 2 out of 8 subjects experience a Grade ≥3 treatment-related AE within 7 days of the subjects receiving the study drug in either TJ003234 arm and no more than 4 out of 16 subjects experience a Grade ≥3

treatment-related AE within 7 days of the subjects receiving the study drug in both TJ003234 arms combined, Part 2 will be initiated. The end of Part 1 is defined as 30 days after the last subject is dosed, or until study termination.

Enrolled subjects will complete follow-up visits for 30 days after dosing to assess the safety and efficacy of the study drug. Subjects will be followed until the complete all study visits, the subject (or their legally authorized representative (LAR)) withdraws consent, the subject is lost to follow-up or the subject dies.

3.1.2. Part 2

Part 2 is designed as a randomized, double-blind, placebo-controlled, 2-arm, parallel-group study to evaluate the efficacy and safety of TJ003234 in subjects with severe COVID-19. Part 2 contains two phases, the first phase, Phase 2, will enroll 120 subjects and the second phase, Phase 3, will enroll approximately 450 subjects. The data collected from Phase 2 will be used to make decision for Phase 3 and may be used to re-estimate sample size of Phase 3 portion. Potential subjects will be screened to assess their eligibility to enter the study within 3 days prior to the first dose administration. A total of 570 eligible subjects will be randomized at a ratio of 2:1 to receive either a single dose of TJ003234 or placebo, administered by intravenous infusion. Randomization will be stratified by age at randomization (<60 years versus ≥ 60 years) and use of remdesivir (yes versus no). Before and after the treatment, all subjects will be allowed to receive supportive care and/or additional treatments for COVID-19 and its complications per the Investigator.

Enrolled subjects will complete follow-up visits for 30 days after dosing to assess the safety and efficacy of the study drug. Subjects will be followed until they complete all study visits, the subject meets the withdrawal criteria in Section 4.4 or the subject dies.

3.1.2.1. Pharmacokinetic (PK) and Anti-Drug Antibody (ADA) Subgroup

In Part 2 Phase 2 stage, 40 subjects will be randomly assigned to a subgroup to collect PK and ADA samples. PK samples will be collected on Day 1 (predose and at End of Infusion), Day 7 and Day 14. ADA samples will be collected on Day 1 predose and Day 14. Of these 40 subjects, 30 will be from the 6 mg/kg TJ003234 treatment arm and 10 will be from the placebo arm.

In Part 2 Phase 3 stage, 40 subjects will be randomly assigned to a subgroup to collect PK and ADA samples. PK samples will be collected on Day 1 (predose and at End of Infusion), Day 7 and Day 14. ADA samples will be collected on Day 1 predose and Day 14. Of these 40 subjects, 30 will be from the 10 mg/kg TJ003234 treatment arm and 10 will be from the placebo arm.

3.1.3. Study Populations and Sample Size

Part 1 of the study will enroll up to 24 subjects at a 1:1:1 ratio (3 mg/kg TJ003234 to 6 mg/kg TJ003234 to placebo). Part 2 of the study will enroll up to 570 subjects at a 2:1 ratio (TJ003234 to placebo).

3.2. Scientific Rationale for Study Design

GM-CSF, as a key upstream trigger factor in the inflammatory cytokine cascade, can enhance the effects of neutrophils and macrophages, produce inflammatory cytokines and activate the phagocytosis. In addition, GM-CSF is also an important cytokine that induces the polarization of monocytes to the inflammatory M1 phenotype and promotes the activation of macrophages, and the macrophages secrete a large number of inflammatory cytokines such as IL-6 and TNF-α, to involve in tissue inflammation (Hamilton, 1980). The strong proinflammatory effects of GM-CSF make it a promising target in acute inflammatory conditions where elevated GM-CSF has been implicated in orchestrating a cytokine storm. At least three such syndromes share immunological and pathologic features of a cytokine storm: chimeric antigen receptor (CAR)-T cell therapy related cytokine release syndrome (CRS), macrophage activation syndrome (MAS) and most recently, acute respiratory distress syndrome (ARDS) in severe coronavirus disease (COVID-19) cases caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).

In the recent COVID-19 epidemic caused by the coronavirus SARS-CoV-2 in China, approximately 15-30% of severe COVID-19 patients developed ARDS (Wang, 2020; Huang, 2020; Chen, 2020; Guan, 2020). Without intervention, the clinical course is expected to be dire for severe COVID-19 patients. Therefore, there is a huge unmet medical need of therapy for severe COVID-19 patients. At present, there is no specific immune modulating therapy for severe COVID-19 patient.

The clinical features (Huang, 2020) and immunopathology (Xu, 2020) of patients with COVID-19 in China have now been reported, and they remarkably resembled those found in SARS (Channappanavar, 2017). Common features among COVID-19 patients, particularly those seriously or critically ill, included lymphopenia and significantly elevated levels of inflammatory cytokines including IL-1, IL-7, IL-8, IL-9, IL-10, basic FGF, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1A, MIP-1B, PDGF, TNF-α, and VEGF. (Huang, 2020). Massive production of IL-6, CRP, D-dimer and ferritin were also observed, which are all indicative of cytokine storm (Wang, 2020). Importantly, lung pathology revealed heavy interstitial lymphocytic infiltrates along with diffuse alveolar damage with fibromyxoid exudates, multinucleated giant cells and hyaline membrane formation, indicative of ARDS (Xu Z, 2020). Interestingly, these pathological features and lung CT imaging characteristics are also remarkably similar to those reported for a subset of JIA patients that developed MAS that led to severe immunopathology and lung disease (Schulert, 2019).

It seems evident from the recent reports that severe COVID-19 bears all the hallmarks of a cytokine storm instigated by exuberant immune cells producing GM-CSF and IL-6. They drive aberrant monocyte and T cell activation which in turn produce more cytokines and chemokines in a feed forward cycle that culminates in profound tissue injury, airway constriction, vascular collapse and organ failure (Zhou, 2020). Peripheral blood mononuclear cell (PBMC) immunophenotyping showed an abundance of highly active GM-CSF-producing T helper cells and pathogenic monocytes in COVID-19 patients (Xu, 2020; Zhou, 2020). A recent study published in Blood showed that GM-CSF antibodies have been demonstrated to effectively inhibit the cytokine storm caused by CAR-T cell therapy and reduce the levels of a series of inflammatory factors such as IFN-g, IL-6, MCP-1, MIP-1 in preclinical experiments. In addition,

it can control the infiltration of immune cells such as T cells and macrophages into the central nervous system, and effectively inhibit the generation of neurotoxicity. Compared to tocilizumab that has been widely used to treat cytokine storm caused by CAR-T cells, GM-CSF antibodies may have better efficacy, especially in regulating the broad spectrum of cytokines and inhibiting neurotoxicity. Therefore, two clinical trials will be conducted to evaluate the therapeutic effects of GM-CSF antibodies or GM-CSF receptor antibodies on CAR-T cell-induced side effects such as cytokine storm and neurotoxicity (Gilead, 2020). Currently, based on the experience of IL-6R antibody tocilizumab in managing CAR-T induced CRS, tocilizumab is being tested for reducing cytokine storm and its complications in a clinical trial of COVID-19 patients in China (Chinese Clinical Trial Registry, n.d.). GM-CSF neutralizing antibody such as TJ003234 may also has the potential to prevent or curb cytokine storm and immunopathology and thus earn more time for viral clearance, which may improve the overall clinical outcome of COVID-19 severe patients.

3.3. Justification for Dose

In this study, the dose of TJ003234 has been predicted based on the results of safety, pharmacokinetics and pharmacodynamics from a single ascending dose study in healthy subjects, preclinical data, the safety data of similar GM-CSF antibodies in patients with rheumatoid arthritis, as well as the data of IL-6 antibody tocilizumab for treatment of cytokine storms. For TJ003234, a single dose escalation study in 32 healthy subjects has been completed. No dose limiting toxicity (DLT) was observed in the 0.3 mg/kg, 1 mg/kg, 3 mg/kg and 10 mg/kg dose groups. The maximum tolerated dose (MTD) was not reached. The half-life of TJ003234 was approximately 3 weeks and plasma concentrations increased proportionally with the dose over the range 0.3 mg/kg to 10 mg/kg. Pharmacodynamics showed similar levels of inhibition of ex-vivo GM-CSF-activated pSTAT5 at doses of TJ003234 3 mg/kg and 10 mg/kg. Inhibition of more than 90% was reached at 4 hours after dosing and was maintained for 2 weeks (full clinical study report submitted to FDA in January 2020).

The dosing regimen of TJ003234 in the Part 2 Phase 3 trial is amended as 10 mg/kg TJ003234 or placebo based on the observed efficacy, safety, and PK data in the completed Part 2 Phase 2 study. In Part 2 Phase 2 study with patients with Covid-19, improved efficacy over the placebo arm was observed with an acceptable toxicity profile of TJ003234. At the same time, increased clearance of TJ003234 (0.02 L/hr in patients with Covid-19 compared to 0.009 L/hr in healthy subjects) was observed at a single dose of 6 mg/kg TJ003234, with a shorter half-life (6 days) than in healthy subjects (3 weeks). Therefore, a single dose of 10 mg/kg is expected to further improve the magnitude of efficacy improvement by providing higher exposure than that of 6 mg/kg dose in Covid-19 patients. Based on the observed PK data, the exposure of a single dose of 10 mg/kg TJ003234 in patients with Covid-19 is expected to be lower than that in healthy subjects. Therefore, an acceptable safety profile is expected to be maintained, as the 10 mg/kg has been tested in healthy subjects with excellent safety profile. The dosing regimen of TJ003234 in the Part 2 Phase 3 trial is amended as 10 mg/kg TJ003234 or placebo based on the observed efficacy, safety, and PK data in the completed Part 2 Phase 2 study.

According to the preclinical toxicology study (Q1W for 4 weeks), the No-Observed-Adverse-Effect Level (NOAEL) dose in Cynomolgus monkeys was 60 mg/kg. Since molecular weight of

TJ003234 is >100,000 Da (146KDa) and administered intravenously, according to FDA guidance stating that proteins administered intravascularly with molecular weight >100 KDa should be normalized to mg/kg as an exception to mg/m2 scaling approach (CDER, 2005), the calculated Human equivalent dose (HED) based on NOAEL is also 60 mg/kg.

GM-CSF antibodies have been reported to be well tolerated in clinical trials. Namilumab and KB003 are drugs with the same mechanism of action as the study drug and both were well tolerated at doses of 5-6 mg/kg (Huizinga, et al., 2017). The Phase IIb clinical trial of mavrilimumab, which is an antibody of GM-CSF receptor and has a similar mechanism of action as the study drug, showed no adverse reactions in the lung (Burmester et al., 2017). The autoantibodies of GM-CSF are associated with the development of idiopathic autoimmune pulmonary alveolar proteinosis (PAP). There is a theoretical risk of developing PAP when therapeutic antibodies targeting GM-CSF are used. Non-clinical studies of mavrilimumab, a compound targeting GM-CSF receptor, showed that macrophage change in lung tissues was only observed in studies with dosing lasting more than 11 weeks (Ryan et al., 2014). Therefore, it is believed that the PAP is a long-term chronic development process and, the risk of PAP developed from drug exposure after a single dose is most likely to be low. In addition, we closely monitored pulmonary function up to 90 days and no clinical meaningful changes of pulmonary function was observed in the single dose escalation study (full clinical study report submitted to FDA in January 2020), Taken together with the safety data in human and preclinical studies, we believe that a single dose of 3 mg/kg and 6 mg/kg TJ003234 will be safe in the patient population.

Preclinical pharmacodynamics showed a treatment effect of <50% (as measured by an inhibitory effect on the GM-CSF/GM-CSFR signaling pathway) at a single intravenous infusion dose of 3 mg/kg in the CIA (type II collagen-induced arthritis) model in cynomolgus monkeys. The results from the in vitro monocyte activation assay to mimic the COVID-19 viral stimulation of primary monocytes confirmed that treatment of 10 μg/ml TJ003234 suppressed the pro-inflammatory cytokine production and activation marker expression, indicating that the dose of 3 mg/kg may be efficacious since the trough concentration of a single dose of 3 mg/kg exceeds 10 μg/ml in the Phase I clinical trial. On theoretical grounds, the GM-CSF levels will further increase in COVID-19 patients with cytokine storms compared to healthy individuals and patients with autoimmune diseases. This hypothesis has been verified by the clinical data of tocilizumab. The mean peak concentration of tocilizumab in patients with cytokine storms caused by CAR-T was 41% lower than that in patients with systemic JIA, suggesting that tocilizumab was eliminated more rapidly in patients with cytokine storms (Le et al., 2018). Therefore, sufficient exposure of TJ003234 will be required to effectively reduce GM-CSF levels and thus their downstream cytokine levels. Therefore, in order to better assess the dose response of TJ003234 in COVID-19 severe patients, and determine an optimal dose for further development, we plan to include an additional dose level of 6 mg/kg TJ003234. Based on the PK from healthy adults, TJ003234 PK appears to be linear and we expect that a single dose of 6 mg/kg may produce two-fold of drug exposure following a single dose of 3 mg/kg TJ003234, which will remain within the range of drug exposure tested to be safe in the FIH.

Overall, the totality of the data from the non-clinical data and clinical data from the single ascending dose escalation study supports 3 mg/kg and 6 mg/kg as safe doses with potential efficacy to be administered in COVID-19 patients. Furthermore, the observed efficacy, safety,

and PK data in the completed Part 2 Phase 2 study support a single dose of 10 mg/kg TJ003234 in the subsequent Part 2 Phase 3 trial as a safe dose with potentially further improved efficacy.

3.4. Criteria for Termination of Study

During the conduct of the study, if the investigator or the sponsor finds that continuation of the trial may cause potential harm to subjects, or the study is futile per IDMC's assessment, the decision may be made to terminate the trial after consultation between the investigator, medical monitor and the sponsor.

4. Selection of Study Populations

4.1. Inclusion Criteria

1. Age: 18 years or older (including 18 years); male or female
2. Laboratory-confirmed SARS-COV-2 or COVID-19 infection as determined by polymerase chain reaction (PCR) or other commercial or public health assay.
3. Bilateral lung infection confirmed by imaging
4. Severe disease that meets one of the following conditions:
    i. At rest, finger blood oxygen saturation ≤ 93% or PaO2/FiO2 ≤ 300 mmHg; OR
    ii. Requiring high flow oxygen ≥ 15L/min
5. Subjects or LARs who are willing to participate in this study and sign the informed consent voluntarily.
6. Be willing to follow the contraception guidelines in Appendix 1
7. Subject has been hospitalized for no more than 5 calendar days at the time of screening.

4.2. Exclusion Criteria

1. Any previous and/or current clinically significant disease or condition that has not been stable within 3 months prior to enrollment, or acute illness, planned medical/ surgical procedure, or any trauma that occurred within 2 weeks prior to enrollment, which, in the opinion of the investigator, may place the subject at risk if participating in the study, or may interfere with the assessment of the study drug or confound interpretation of the study results, or affect the patient's ability to participate in the study independently.
2. ***Applies to Part 1 only:*** Chronic obstructive pulmonary disease (COPD) and moderate/severe asthmatic patients requiring inhaled corticosteroid, long-acting beta-adrenergic agonists, long-acting anticholinergics, or long-term oxygen therapy. Mild asthmatic patients treated with short-acting beta-adrenergic agonists and/or low dose of inhaled corticosteroid and/or long-acting beta-adrenergic agonists are considered eligible. Please refer to Appendix 4 for inhaled cortiscoteroids dose guidance.
3. Pulmonary interstitial disease, pulmonary alveolar proteinosis, and pulmonary granulomatosis.

4. Cardiovascular event in the 3 months prior to study drug administration: acute myocardial infarction or unstable angina pectoris, severe arrhythmia (multiple sources of frequent ventricular premature beat, ventricular tachycardia and ventricular fibrillation); New York Heart Association Classification (NYHA): Class III-Class IV.
5. Severe renal impairment: e.g. eGFR ≤30 ml/min estimated by MDRD equation or have received treatments such as kidney transplantation and dialysis.
6. Subjects that cannot adhere to protocol requirements due to neuropsychiatric disorders.
7. Severe liver disease: e.g. Child-Pugh Score for Cirrhosis as (Grade C, elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (> 5 × upper limit of normal.
8. Known active or chronic hepatitis B or C infection or human immunodeficiency virus (HIV).
9. Known active tuberculosis (TB), history of incompletely treated TB, suspected or known extrapulmonary TB, suspected or known systemic bacterial or fungal infections.
10. Blood system disorders or routine blood analysis test abnormalities:
    - Hemoglobin < 8 g/dL;
    - ANC <1500 × 10^9/L;
    - Platelets < 50 × 10^9/L.
11. Dependence on glucocorticoid treatment equivalent to methylprednisolone 2 mg/kg/ day or more or long-term use of anti-rejection or immunomodulatory drugs.
12. Subjects that require invasive mechanical ventilation or ECMO.
13. Pregnant or breastfeeding females.
14. Have received any live vaccination within 30 days before dosing.
15. Subjects who, in the opinion of the investigator, are not suitable for participation in this clinical study or will not agree to follow the institution's supportive care protocol. Any condition that, in the opinion of the investigator, may increase the risk associated with the subject's participation in the study or may interfere with the assessment of the study drug or confound the interpretation of the study results.

4.3. Subject Numbering

Three-digit subject numbers will be allocated as all subjects consent to take part in the study. Subject numbers in Part 1 will follow the pattern "1yy". Subject numbers in Part 2 will follow the pattern with "2yy" and "3yy". Within each study site, this number will be allocated to subjects according to the sequence of presentation for trial participation. The subject number will be combined with the 4-digit site number ("xxxx") to form the unique 7-digit subject identifier ("xxxx-1yy" for subjects in Part 1 and "xxxx-2yy" for subjects in Part 2 Phase 2 and "xxxx-3yy" for subjects in Part 2 Phase 3) for the study. This subject ID number will also be used as a unique identifier for the subject throughout the study for lab reports, source, safety reporting forms, case

report forms (CRFs), etc.

4.4. Withdrawal Criteria

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn if any of the following criteria are met:

1) Subject withdraws informed consent
2) Subject is lost to follow-up after the investigator or designee has made multiple documented attempts to regain contact with the subject, including at least two attempts by telephone and a final attempt by certified or traceable mail.

Prior to withdrawal, subjects should be encouraged to complete all follow-up assessments if possible. Subjects with ongoing adverse events at the time of withdrawal should be followed in accordance with Section 7.1.5.

5. Study drug

The study drug, TJ003234, is provided by I-Mab Biopharma Co., Ltd., and should only be used for this study according to the study protocol and Pharmacy Manual. Placebo will be 0.9% sodium chloride injection (normal saline) and must be provided by the site.

5.1. Physical and chemical properties, specifications and ingredients of drugs

TJ003234 is a recombinant anti-GM-CSF humanized monoclonal antibody, consisting of two heavy chains and two light chains of IgG1. Each heavy chain contains 450 amino acids and each light chain contains 214 amino acids. Its theoretical molecular weight is about 146 kDa.

TJ003234 is a brown-yellow sterile liquid, with a specification of 200 mg/2 ml/ vial. Its ingredients contain 100 mg/ml TJ003234, 0.96 mg/ml L-histidine, and 2.89 mg/ml L-histidine hydrochloride, 75.31 mg/ml sucrose, 0.2 mg/ml polysorbate 80 (pH 5.8).

The drug TJ003234 should be stored and transported at 2-8°C, protected from light.

5.2. Drug Packaging, Labelling, and Storage

TJ003234 drug product is packaged in a 2 ml type I glass vial, stoppered with 13 mm bromobutyl rubber stopper (Aptar Stelmi) and capped with aluminum cap. Vials of TJ003234 will be packaged in cartons. Each vial and carton will contain a label stating the study number, lot number, date of manufacture, drug type, storage conditions, and appropriate precautionary statements.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
All study treatments must be stored in a secure, environmentally controlled area in accordance with the labeled storage conditions with access limited to the Investigator and authorized clinical center staff.

5.3. Drug Dispensing, Administration and Dosage

5.3.1. Randomization and Blinding

Both parts of this study are randomized, double-blind, and placebo controlled.

Most study personnel will remain blinded for the duration of each Part of the study (i.e., Part 1 will remain blinded until the completion of Part 1, at which point it will be unblinded for exploratory analyses; Part 2 phase 2 will remain blinded until completion of Part 2 phase 2; and Part 2 phase 3will remain blinded until database lock). To allow for the execution of clinical trial-related services, the following individuals will be unblinded during the study:

- External randomization and trial supply management (RTSM) vendor
- Independent Statistician
- External clinical supply distribution vendor
- Bioanalytical laboratory analyst
- Sponsor Drug Supply Management Representative
- Site pharmacy staff
- Unblinded study nurse (if needed for site operations to administer study drug)

5.3.1.1. Part 1

There will be approximately 24 subjects randomized 1:1:1 (eight 3 mg/kg TJ003234: eight 6 mg/kg TJ003234: eight placebo) to the following treatment arms:

- Treatment 1A: TJ003234 3 mg/kg (initial dose assignment based on weight at screening); single dose.
- Treatment 1B: TJ003234 6 mg/kg (initial dose assignment based on weight at screening); single dose.
- Treatment 1C: Placebo (administered as normal saline); single dose.

Randomization will not be stratified. Each investigational site will randomize subjects to treatment groups using a randomization scheme generated by an RTSM system. Treatment allocation will be blinded per Section 5.3.1.

After the safety evaluation and decision has been made to continue to Part 2, the data from Part 1 will be analyzed for exploratory analysis.

5.3.1.2. Part 2

There will be approximately 570 subjects randomized 2:1 (380 TJ003234: 190 placebo) to the following treatments arms:

- Treatment 2A: TJ003234 6 mg/kg (phase 2) or 10 mg/kg (phase 3), with initial dose

assignment based on weight at screening; single dose.

- Treatment 2B: Placebo, administered as normal saline; single dose.

Randomization will be stratified by age at randomization (<60 years versus ≥ 60 years) use of remdesivir (yes versus no). Each investigational site will randomize subjects to treatment groups using a randomization scheme generated by an RTSM system. For more information, please refer to the Pharmacy Manual. Treatment allocation will be blinded per Section 5.3.1.

5.3.2. Drug Dispensing

Once the treatment assignment has been confirmed per Section 5.3.1.1 or Section 5.3.1.2, if the subjects is assigned to a TJ003234 treatment arm, the study drug dose will be calculated according to the body weight of subjects at screening when dispensing. The study drug is diluted to appropriate volume and concentration with 0.9% sodium chloride injection (normal saline) (see Table 4). After dilution with normal saline in the infusion bag, diluted study drug should be fully infused within 4 hours if stored at room temperature, or within 24 hours if stored at 2-8℃ If the subject is assigned to a placebo arm, normal saline will be administered per the Pharmacy Manual.

Table 4. Study drug dispensing dose and volume

Subject weight	Dosing mode	Infusion bag	Specification and total volume of infusion bag
≤ 100 kg	Intravenous drip	Infusion bags	100 mL
100.1 to 250 kg	Intravenous drip	Infusion bags	250mL

For specific instructions on the preparation and management of the study drug, refer to the Pharmacy Manual.

5.3.3. Drug Administration

After pre-dose procedures have been conducted on Day 1, eligible subjects will receive a single dose of their assigned treatment, diluted using normal saline (0.9% NaCl) to the appropriate volume and concentration per Table 4 and the subject's body weight at screening. Administer using a low-protein-binding 0.22 μm in-line filter and an infusion pump. The infusion line should be flushed with 0.9% sodium chloride injection after TJ003234 administration to ensure that the subject receives the full dose. All doses should be administered over 1 hour. Further instructions with details on handling and administration of study drug is described in the separate Pharmacy Manual.

5.4. Compliance Requirements

5.4.1. Contraceptive requirements

Females of childbearing potential and males should agree to take appropriate contraceptive

measures during the trial period and for 4 months after the final dose of study drug. For detailed instructions and definitions, please refer to Appendix 1.

5.5. Concomitant Medication and Therapies

The investigator should record all concomitant medications (including any investigational therapies), indications, daily doses, starting and ending dates of dosing throughout the study.

Medications and therapies administered within 3 days of the first dose of study drug (with the exception of SARS-CoV-2 vaccine history) should be recorded as prior medications or therapies. Medications or therapies received after the first dosing of the study drug should be recorded as concomitant medications or therapies.

5.6. Prohibited Medications

The following prior or concomitant medications are not allowed during the trial:

1. Immunomodulatory/immunosuppressive drugs, including biologics and JAK inhibitors except when administered as a rescue therapy as described in Section 5.7 (Note: recommended drugs for standard treatment are allowed, such as Glucocorticoid).
2. Drugs that may aggravate the subjects' conditions per the investigator's judgement.
3. Any vaccine during the trial or any live vaccine within 30 days prior to dosing, with the exception of the SARS-CoV-2 vaccine.

5.7. Rescue Therapies

Rescue therapies are considered to be any otherwise prohibited medications given for COVID-19 (e.g. convalescent plasma, tocilizumab, etc.) that are administered after the subject has received the study drug and experiences deterioration in their clinical condition. Rescue therapies are permitted after study drug administration at the Investigator's discretion and a deterioration of clinical status must be documented. Prior to administering a rescue therapy, perform the following procedures as an unscheduled visit:

- Clinical Status Assessment
- Arterial Blood Gas Analysis
- SOFA Score
- PaO2/FiO2 ratio
- Physical Examination
- Pulse Oximetry
- Vital Signs
- Clinical Laboratory Tests: CBC, Serum Biochemistry, Troponin, CRP, LDH, Ferritin, Cytokine Levels

6. Study Procedures

This trial will use a 2-part randomized, double-blind, placebo-controlled design and observation for 30 days after a single dose of study drug. The study procedures are described below.

6.1. Description of Study Procedures

6.1.1. Vital signs and Pulse Oximetry

The following vital signs will be measured according to the schedule of procedures: temperature, pulse, respiratory rate and blood pressure.

Vital signs should be monitored and recorded within 30 min before drug infusion, 30 min ± 5 min after the start of infusion, at the end of infusion ± 5 min, and 60 min ± 5 min after infusion.

The measurement of blood pressure and pulse should occur according to institutional practices.

Pulse oximetry should be recorded daily while hospitalized. The lowest registered level from each day should be collected.

6.1.2. Physical examination

A general physical examination should include the overall appearance, head and face, ear, nose, throat, mouth, skin, lymph nodes, respiratory, cardiovascular, abdomen, urogenital (when necessary), musculoskeletal and nervous, and neurological systems. Missed body systems will not be considered a protocol deviation, unless there are ongoing Adverse Events that are not assessed as a result of missed body systems.

6.1.3. ECG

ECGs will be performed as specified in the schedule of procedures according to institutional practices.

During visits where both ECGs and blood draws are scheduled, the ECG should take place before the blood draws.

6.1.4. Clinical laboratory tests

Blood samples will be collected for serum biochemical and hematological analysis. Urine samples will be collected for urinalysis. The investigator shall review the laboratory test results and record laboratory test results with clinical significance as judged by the investigator as an adverse event.

Table 5. Laboratory Tests

Serum biochemical test	• Blood glucose • Liver and kidney functions: Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyltransferase, total protein, albumin, total bilirubin, direct bilirubin, creatinine, eGFR[a], BUN, uric acid. • Serum electrolytes: potassium, sodium, chlorine, calcium, magnesium, inorganic phosphorus.
CBC	• White blood cells, absolute neutrophil count and percentage, absolute lymphocyte count and percentage, absolute monocyte count and percentage, absolute eosinophil count and percentage, absolute basophil count and percentage. • Red blood cells, hemoglobin, hematocrit, mean cell volume • Platelets
Coagulation assessment	• Prothrombin time, International Normalized Ratio • Activated partial thromboplastin time • D-dimer
Urinalysis	• Bilirubin, Blood, Color and appearance, Glucose, Ketones, Leukocyte esterase, Nitrite, pH, Protein, Specific gravity, Urobilinogen • Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)
Other	• β-human chorionic gonadotropin [b] • Follicle-stimulating Hormone (FSH) test [c] • Inflammation-related indicators: troponin, C-reactive protein, LDH, serum ferritin • Arterial blood gas analysis: pH, partial pressure of oxygen, partial pressure of carbon dioxide, total carbon dioxide, oxygen saturation, actual bicarbonate, standard bicarbonate, base excess, anion gap • SARS-CoV-2 diagnostic test by PCR or other commercial or public health assay. Note that a standardized method should be used for collection of nasopharyngeal samples. Please use the same nostril for collections if only one nostril will be sampled. • Cytokines, such as IL-1RA, IL-1β, IL-2, IL-6, IL-7, IL-10, GCSF, GM-CSF, CCL2, CCL3, CCL17, CXCL10, TNF-α and IFN-γ • Pharmacokinetic Sampling (for those in the PK/ADA subgroup in Part 2) • ADA Sampling (for those in the PK/ADA subgroup in Part 2)

a. eGFR(ml/min×1.73m^2) =175×creatinine ([Scr(mg/dL)])$^{-1.154}$×age$^{-0.203}$×gender (male=1, female =0.742)×1.212 (if black) ;

b. Serum pregnancy test for women of childbearing potential at the time of screening.

c. If needed to confirm menopausal status.

6.1.5. Radiographic Lung Imaging

Radiographic lung imaging includes lung CT or chest X-ray. If this procedure was performed as standard of care in the 14 days prior to Day 1 and radiographic infiltrates are present, this may be used, and imaging is not required at Screening or Day 1.

6.1.6. Pregnancy test

A blood pregnancy test will be performed for women of childbearing potential at screening. Pregnant women are not eligible to participate in this study and will be considered ineligible for screening.

6.1.7. Adverse Events (AEs)

The investigator should collect and record AEs for each subject from the signing of the informed consent to 30 days after the last dose. The investigator is responsible for observation, recording and follow-up of all AEs that occur during the study, regardless of any cause. Serious adverse events (SAEs) that occur within 30 days after the last dose should also be collected and reported if considered as related to TJ003234 by investigator (see Section 7.2.3 for the reporting process). The investigator will follow up AEs as specified in Section 7.

6.2. Screening period (Day -3 to Day -1)

Subjects (or LAR) should sign a written or electronic ICF on a voluntary basis before screening. The screening is performed within Day -3 to Day -1, to identify if they meet the inclusion/exclusion criteria. Those subjects who meet all inclusion criteria and do not meet any one of the exclusion criteria are eligible to participate in this trial. The screening procedures include the following:

- Demographic data (including gender, age, ethnicity, date of birth);
- Height and body weight;
- Medical history from previous 5 years, including smoking history. Ensure that the date of onset of COVID-19 symptoms is recorded as part of the Medical History;
- SARS-CoV-2 vaccine history (not restrictive to within 3 days before dosing);
    - Number of doses
    - Date of dose(s)
    - Brand name
- Collecting a complete history of prescription or over-the-counter drugs, dietary supplements and herbal medicines used within 3 days before dosing;
- Physical examination;
- 12-lead ECG;
- Vital signs;
- PaO2/FiO2 ratio;
- Radiographic lung imaging (chest x-ray or CT) (see section 6.1.5);
- Biological samples are collected for the following tests. If any of these labs were drawn prior to subject signing consent, but within 72 hours of dosing, they may be used for the purposes of this visit and they do not need to be repeated:
    - Safety laboratory tests (CBC, blood biochemistry test, urinalysis);
    - Coagulation function test (prothrombin time (PT), activated partial prothrombin time (APTT), international normalized ratio, D-dimer);
    - Blood β-HCG testing (required for female subjects of childbearing potential only);

  - FSH test (to confirm menopausal status, if applicable)
  - Testing of C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH) and serum ferritin;
  - SARS-CoV-2 diagnostic test by PCR or other commercial or public health assay. If a subject has a positive test within the 14 days prior to study drug administration, this may be used to assess eligibility, and an additional test at screening does not need to be performed. Note that a standardized method should be used for collection of nasopharyngeal samples. Please use the same nostril for collections if only one nostril will be sampled.
  - Arterial blood gas analysis;
  - Testing of cytokine levels.
- Pulse oximetry;
- Collection/evaluation of adverse events at baseline.
- Review subject eligibility

6.3. Baseline period (Day 1)

Subjects will complete the following procedures before dosing:

- Review any changes in subject's status since screening to confirm eligibility;
- Physical examination;
- Biological samples are collected for the following tests:
  - Safety laboratory tests (routine blood analysis, blood biochemistry test, urinalysis);
  - Coagulation function test (PT, aPTT, INR, D-dimer);
  - Arterial blood gas analysis (may be omitted if screening test was done within 24 hours);
  - Troponin test;
  - Testing of CRP, LDH and serum ferritin;
  - Testing of cytokine levels.
  - PK and ADA sampling (if included in the PK/ADA subgroup in Part 2)
- Vital signs;
- PaO2/FiO2 ratio;
- 12-lead ECG;
- Pulse oximetry;
- Record baseline respiratory support requirements (e.g., oxygen requirements)
- Clinical status assessment;

- SOFA score.

If dosing occurs within 24 hours of screening, pre-dose procedures do not need to be repeated, unless the labs are from within >24 hours of dosing. The following procedures must be completed Predose, as they were not completed as screening assessments:

- SOFA score
- Clinical Assessment
- Troponin test

After completing the above procedures, subjects will be randomized and receive their assigned study drug by IV infusion.

During the infusion, vital signs will be measured in accordance with Section 6.1.1. After end of infusion, the following procedures will be performed:

- Vital signs;
- 12-lead ECG;
- Collection/evaluation of adverse events;
- Monitoring concomitant medication/treatment.

After the infusion, the following procedure will be performed within 15 minutes of end of infusion:

- PK sampling (for those subjects in the PK/ADA subgroup in Part 2)

6.4. Follow-up period: Day 2

The following procedures will be performed:

- Vital signs;
- Physical Examination;
- Biological samples are collected for the following tests:
  - Safety laboratory tests (routine blood analysis, blood biochemistry test, urinalysis);
  - Coagulation function test (PT, aPTT, INR, D-dimer);
  - Testing of CRP, LDH and serum ferritin;
  - Testing of cytokine levels.
- Pulse oximetry
- Collection/evaluation of adverse events;
- Monitoring concomitant medication/treatment.

6.5. Follow-up period: Day 3

The following procedures will be performed

- Vital signs;

- Physical Examination;
- Biological samples are collected for the following tests:
  - Safety laboratory tests (routine blood analysis, blood biochemistry test, urinalysis);
  - Coagulation function test (PT, aPTT, INR, D-dimer);
  - Testing of CRP, LDH and serum ferritin;
  - Testing of cytokine levels.
- Pulse oximetry
- Collection/evaluation of adverse events
- Monitoring concomitant medication/treatment

6.6. Follow-up period: Day 5

The following procedures will be performed:

- Vital signs;
- Physical Examination;
- Biological samples are collected for the following tests:
  - Safety laboratory tests (routine blood analysis, blood biochemistry test, urinalysis);
  - Coagulation function test (PT, aPTT, INR, D-dimer);
  - Testing of CRP, LDH and serum ferritin;
  - Testing of cytokine levels.
- Pulse oximetry
- Collection/evaluation of adverse events
- Monitoring concomitant medication/treatment

6.7. Follow-up period: Day 7

If subjects are discharged prior to this visit, the visit may occur as an outpatient or telephone visit. If the visit occurs via telephone, only collection/evaluation of adverse events, clinical status assessment (including whether subject is still on supplemental oxygen support), and monitoring concomitant medication and treatment must occur. The following procedures will be performed:

- Vital signs;
- Physical Examination;
- Biological samples are collected for the following tests:
  - Safety laboratory tests (routine blood analysis, blood biochemistry test, urinalysis);
  - Coagulation function test (PT, aPTT, INR, D-dimer);
  - Arterial blood gas analysis (not needed if conducted as an outpatient visit);

- Troponin test;
- Testing of CRP, LDH and serum ferritin;
- SARS-CoV-2 diagnostic test by PCR or other commercial or public health assay
- Testing of cytokine level.
- PK sampling (for those subjects in the PK/ADA subgroup in Part 2)

- 12-lead ECG;
- PaO2/FiO2 ratio (not needed if conducted as an outpatient visit)
- Pulse oximetry
- Radiographic Lung Imaging;
- Clinical status assessment;
- SOFA score (not needed if conducted as an outpatient visit);
- Collection/evaluation of adverse events;
- Monitoring concomitant medication/treatment.

6.8. Follow-up period: Day 11 ± 1

If subjects are discharged prior to this visit, this visit may occur via telephone. If the visit occurs via telephone, only collection/evaluation of adverse events, and monitoring concomitant medication and treatment must occur. Otherwise, the following procedures will be performed:

- Vital signs;
- Pulse oximetry;
- Collection/evaluation of adverse event
- Monitoring concomitant medication/treatment

6.9. Follow-up period: Day 14 ± 2

If subjects are discharged prior to this visit, the visit may occur as an outpatient or telephone visit. If the visit occurs via telephone, only collection/evaluation of adverse events, clinical status assessment (including whether subject is still on supplemental oxygen support), and monitoring concomitant medication and treatment must occur. The following procedures will be performed:

- Vital signs;
- Physical Examination;
- Biological samples are collected for the following tests:
  - Safety laboratory tests (routine blood analysis, blood biochemistry test, urinalysis);
  - Coagulation function test (PT, aPTT, INR, D-dimer);
  - Arterial blood gas analysis; (not needed if performed as an outpatient visit);

  - Troponin test;
  - Testing of CRP, LDH and serum ferritin;
  - SARS-CoV-2 diagnostic test by PCR or other commercial or public health assay
  - Testing of cytokine levels
  - PK and ADA sampling (if included in the PK/ADA subgroup in Part 2)
- 12-lead ECG;
- PaO2/FiO2 ratio (not needed if conducted as an outpatient visit)
- Pulse oximetry
- Radiographic lung imaging;
- Clinical status assessment;
- SOFA score (not needed if conducted as an outpatient visit);
- Collection/evaluation of adverse events;
- Monitoring concomitant medication/treatment.

6.10. Follow-up period: Day 30± 2 (End of Study Visit)

If subjects are discharged prior to this visit, this visit may occur as an outpatient visit or via telephone. If the visit occurs via telephone, only collection/evaluation of adverse events, clinical status assessment (including whether subject is still on supplemental oxygen support), and monitoring concomitant medication and treatment must occur. Otherwise, the following procedures will be performed:

- Vital signs;
- Physical Examination;
- Biological samples are collected for the following tests:
  - Safety laboratory tests (routine blood analysis, blood biochemistry test, urinalysis);
  - Coagulation function test (PT, aPTT, INR, D-dimer);
  - Arterial blood gas analysis (not needed if conducted as an outpatient visit);
  - Testing of CRP, LDH and serum ferritin;
  - SARS-CoV-2 diagnostic test by PCR or other commercial or public health assay
  - Testing of cytokine levels.
- 12-lead ECG;
- PaO2/FiO2 ratio (not needed if conducted as an outpatient visit);
- Pulse oximetry;
- Radiographic lung imaging;
- Clinical status assessment;

- SOFA score (not needed if conducted as an outpatient visit);
- Collection/evaluation of adverse events;
- Monitoring concomitant medication/treatment.

6.11. Discharge from Hospital

If a subject is discharged from the hospital prior to the end of study visit, an unscheduled arterial blood gas analysis, PaO2/FiO2 ratio, and a SOFA score should be completed based on the last arterial blood gas analysis performed while the subject was hospitalized.

7. Safety and Reporting

7.1. Adverse Events

Adverse events observed or discovered by the Investigator or those reported by subjects, regardless of having a suspicious causal relationship with the study drug or not, must be recorded according to the following requirements.

7.1.1. Definition of Adverse Events

An adverse event (AE) is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial whether or not the event is considered related to the study drug. Disease progression or deterioration must also be recorded as an AE/SAE, regardless of whether the Investigator assesses that it is related to the study drug. Additionally, signs and symptoms from the following may be considered AEs: drug overdose, withdrawal or misuse, drug interactions, extravasations, exposure during pregnancy/breastfeeding.

7.1.2. Collection of Adverse Events

The Investigator should report all adverse events using concise medical terminologies. Disease diagnosis should be given as much as possible rather than listing symptoms and signs only.

The Investigator should collect and record adverse events for all subjects from the signing of the informed consent to 30 days after the last dose or the subject meets the withdrawal criteria in Section 4.4. The Investigator is responsible for observation, recording and follow-up of all adverse events that occur during the study, regardless of any cause. SAEs that occur after 30 days of the last dose or after a withdrawal criteria is met should also be collected and reported (see 7.2.4 for the reporting process) if judged to be possibly related to the study drug by the investigator.

For any adverse event that occurs during this trial, regardless of seriousness and relatedness, the Investigator should record them in the CRF, including the occurrence date, symptoms, severity (CTCAE), even start and stop dates, action taken with the study drug (no action taken, stopped temporarily, permanently discontinued or N/A), treatment methods and outcomes (resolved, resolved with sequelae, not resolved, resolving, fatal, or unknown), etc. In addition, based on a comprehensive consideration of the disease itself, comorbidities, and concomitant

medications/therapies, its causal relationship with the study drug should be evaluated.

The Investigator should determine whether the abnormal laboratory test result is clinically significant or not. If the abnormal laboratory test value is clinically significant, it should be recorded as an adverse event on the original medical records and CRFs.

If unexplainable, abnormal laboratory test results occur, repeated tests or follow up should be performed until the test results are within the normal range or at the baseline level and/or the abnormal results are reasonably and adequately explained and recorded on the original medical records and CRFs.

If any new infections occur regardless of the infection agent (i.e., viral or non-viral), they should be recorded as AEs. Additionally, in the CRF, the site of infection and source of culture (bronchoalveolar lavage, tracheal aspirate, sputum, blood, urine, etc.,) should also be recorded.

7.1.3. Criteria for severity of adverse events

The severity of adverse events is judged per CTCAE version 5.0 standard, divided into the following 5 grades:

- Grade 1- Mild, requiring no treatment or requiring minimal, non-invasive treatment only.
- Grade 2- Moderate, requiring a general degree of non-invasive treatment.
- Grade 3- Serious, resulting in limited daily activities.
- Grade 4- Symptoms that may be life-threatening, leading to limited daily activities, or permanent injury and disability.
- Grade 5- Death.

7.1.4. Criteria for determining causality between adverse events and study drug

The investigator will determine the causality between adverse events and the study drug according to the correlation between them, and divide them into five categories, they are “definitely related, probably related, possibly related, unlikely related, definitely unrelated”. “Definitely related, probably related, and possibly related” are classified into related to the study drug, and “unlikely related, definitely unrelated” are classified into unrelated to the study drug.

- Definitely unrelated

AE is definitely not related to the use of study drug.

- Unlikely related

AE is more likely to be caused by other factors such as concomitant medications or concomitant disease, or the temporal relationship indicates that it is unlikely to be causally related to the study drug.

- Possibly related

AE may be related to the study drug. Other factors such as concomitant medications or concomitant disease have not been identified yet. There is a reasonable temporal relationship between the AE and study drug; therefore, a causal relationship is not ruled out.

- Probably related

AE may be related to the drug use. There is indicative temporal relationship (for example, determined by study drug discontinuance). It is unlikely to be caused by other factors such as concomitant medications or concomitant disease.

- Definitely related

AE is a possible adverse reaction and cannot be explained by other reasons, such as concomitant medications and concomitant disease. There is an obvious temporal relationship between the AE and the study drug (for example, it can be determined by study drug discontinuance and rechallenge).

7.1.5. Follow-up of Adverse Events

All adverse events (including abnormal laboratory test results) must be followed up until the end of the study or any one of the following conditions has been achieved, whichever occurs later:

- The event has resolved;
- The event is stable;
- The event returns to the baseline level;
- The event is judged as not treatment-related by investigator;
- When more information is not available (subject withdrew consent and/or refuses to provide more information, is lost to follow up or dies);
- The investigator determines that further follow-up is not warranted.

7.2. Serious Adverse Events (SAEs) and Adverse Event of Special Interest (AESI)

7.2.1. Definition of SAE

An AE that meets any one of the following conditions, regardless of whether related to study drug or not, should be considered a serious adverse event:

1) Results in death;
2) Is life-threatening (i.e., the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death);
3) Causes inpatient hospitalization or prolongation of existing hospitalization;
4) Results in persistent or significant disability/incapacity;
5) Is a congenital anomaly or birth defect (in the child of a subject who was exposed to the study drug);

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalized:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalizations planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

7.2.2. Adverse Event of Special Interest (AESI)

This study will consider the following AEs to be AESIs:

- Infusion-related reactions at grade 3 or higher
- Grade 3 or higher infections
- Pulmonary alveolar proteinosis.

These AESIs may not meet the criteria of an SAE, but the investigator shall report them according to the reporting requirements and timeframe of SAEs (i.e., the investigator shall fill out the *Serious Adverse Event Report Form* as soon as possible (within 24 hours) after becoming aware of the AESI, and follow up the outcome of the event. If the IRB has any reporting requirements for the AESI, the investigator shall report them in accordance with relevant IRB requirements (if applicable).

7.2.3. Reporting of SAEs and AESIs

Any SAE or AESI, which occurs to any subject participating in this study must be reported by investigator to the sponsor within 24 hours (and IRB as required) of first becoming aware of the event. The study sponsor will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

SAEs will be collected by the investigator from the time of consent through 30 days after the last dose of study drug or the subject meets the withdrawal criteria in Section 4.4. Any SAE that is judged by the investigator to be related to the study drug must be reported regardless of the amount of time since the last dose received. Follow-up information collected for any initial report of an SAE must also be reported to the sponsor (or its designee) within 24 hours of receipt by

the investigator.

In the event of death, regardless of cause, all attempts should be made to obtain the death certificate and any autopsy report, if performed. These records should be reviewed in detail, and the investigator should comment on any event, lab abnormality, or any other finding, noting whether it should be considered a serious or non-serious AE, or whether it should be considered as part of the subject's history. In addition, all events or other findings determined to be SAEs should be identified on the follow-up SAE form and the investigator should consider whether the event is related or not related to study drug.

7.3. Pregnancy

A pregnancy event refers to pregnancy of a female subject or a male subject's partner during the trial. After becoming aware of the pregnancy, the investigator shall immediately fill out the *Pregnancy Report Form*, and promptly (within 24 hours after becoming aware of the pregnancy) report them to the sponsor or designee (and the IRB, if required). Pregnancy outcomes will be followed by the Sponsor. In addition, the investigator must report to the sponsor or designee follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome.

7.4. Emergency Unblinding

As a double-blind, placebo-controlled study, both the subjects and Investigators are blinded to the study treatment assignment. In addition, it is anticipated that all clinical research personnel, laboratory personnel, except for personnel needed to prepare the study drug, are blinded to the treatment assignment and will remain blinded through the completion of the study.

In the event emergency unblinding of study treatment is necessary, the Investigator shall utilize the RTSM system to obtain subject dose details. The individual subject dose details should be revealed only in case of an emergency where the further treatment of the subject is dependent on knowing the study medication he or she has received. The date and time of breaking the blind as well as the reason must be recorded on the subject study medication record. The subject will be automatically discontinued from the study in the event emergency unblinding of study treatment takes place. If a blind is broken due to an adverse event, a corresponding adverse event entry must be completed in the CRF. Any ongoing AEs will be followed in accordance with Section 7.1.5 of the protocol.

It is strongly encouraged that unblinding only be completed after consultation with the medical monitor, provided this does not compromise subject safety. If unblinding should occur (either by accident or for a medical emergency), the Investigator must promptly and immediately notify the Sponsor, study medical monitor, and IRB/IEC, and document the circumstances surrounding this action in a memorandum to the study file.

8. Data Handling and Recordkeeping

8.1. Data Record and Management

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each subject. The completed original CRFs are the sole property of I-Mab Biopharma and should not be made available in any form to third parties, except for authorized representatives of I-Mab Biopharma or appropriate regulatory authorities, without written permission from I-Mab Biopharma.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the Investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry. In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

8.2. Protocol Deviations

The Investigator must adhere to the protocol as detailed in this document. The Investigator will be responsible for enrolling only those subjects who have met protocol eligibility criteria. The Investigators will be required to sign an Investigator Agreement to confirm acceptance and willingness to comply with the study protocol. The Investigator should document and explain any protocol deviations in source. The Investigator should promptly report any deviations to the Sponsor or designee, and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor or designee will review all protocol deviations and conduct impact assessments as needed. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed and will not be granted.

8.3. Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation/International Council for Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following: signed informed consent documents for all subjects; subject identification code list, screening log (if applicable), and enrollment log; record of all

communications between the Investigator and the IRB; composition of the IRB; record of all communications between the Investigator, Sponsor, and their authorized representative(s); list of Sub investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures; copies of CRFs (if paper) and of documentation of corrections for all subjects; investigational product accountability records; record of any body fluids or tissue samples retained; and all other source documents (subject records, hospital records, laboratory records, etc.).

9. Statistical Considerations

The details of the statistical methods and data presentation, PK and ADA analysis will be provided in the Statistical Analysis Plan (SAP).

9.1. Sample Size Determination

This is a 2-part study. Part 1 will enroll about 24 subjects to establish the safety of TJ003234 in subjects with severe COVID-19 before initiating Part 2.

The estimated rate of mechanical ventilation free subjects in the control arm is based on recent observations in COVID-19 studies.

The sample size of Part 2 Phase 2 portion is calculated based on the following assumptions:

- Randomization ratio of 2:1 (TJ003234 6 mg/kg : placebo);
- Rate of mechanical ventilations free subjects by Day 30: 88% in the TJ003234 arm and 77% in the placebo arm;
- 2-sided alpha of 0.20 and 80% power.
- 10% drop out rate

The sample size of Part 2 Phase 3 portion is calculated based on the following assumptions:

- Randomization ratio of 2:1 (TJ003234 10 mg/kg : placebo);
- Rate of mechanical ventilations free subjects by Day 30: 88% in the TJ003234 arm and 77% in the placebo arm;
- 2-sided alpha of 0.05 and 80% power.
- 10% drop out rate

Part 2 plans to enroll of 570 subjects with 120 in the Phase 2 portion and 450 in the Phase 3 portion. The results of Phase 2 portion may be used to re-estimate the sample size for Phase 3 portion.

9.2. General Considerations

Analysis Populations:

Intent-to-treat (ITT) Population: All randomized subjects. This population will be used for the primary analysis for Part 1 and Part 2 phase 2 portion, and sensitivity analysis of primary analysis for Part 2 phase 3 portion.

Modified Intent-to-treat (mITT) Population: All randomized subjects who are non- mechanical ventilated at baseline. This population will be used for the primary analysis of Phase 2 phase 3 portion.

Safety Population: Includes all subjects who receive the study drug. This safety population will be used for the analysis of demographic data, baseline characteristics, and safety.

Efficacy-evaluable Population: All subjects in the safety population with at least one post-dose efficacy evaluation.

Methods for Statistical Analysis

All data will be summarized by treatment group using descriptive statistics based on the data types by timepoint if applicable. Unless otherwise specified, descriptive statistics for continuous variables will include number of subjects, mean, standard deviation (SD), median, and range. For categorical variables, descriptive statistics including counts and percentages will be reported. All statistical analysis will be performed using SAS 9.4 (or above version) statistical analysis software. The specific statistical method will be detailed in the Statistical Analysis Plan (SAP).

9.3. Subject Demographics/Other Baseline Characteristics

Demographics and baseline characteristics (age, sex, race, ethnicity, and some other baseline disease characteristics) will be summarized for the Safety Population. Descriptive statistics will be presented in addition to data listings.

9.4. Safety Analysis

Safety and tolerability evaluations will be performed for all subjects in the safety population.

Unless otherwise specified, the last evaluation before dosing will be used as the baseline. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

Summary statistics and listings of all the safety data will be provided by treatment group and time points as specified in the schedule of procedures.

9.5. Efficacy Analysis

All efficacy endpoints will be summarized by treatment group with descriptive statistics based on the ITT / mITT / efficacy-evaluable population. 95% CI of the estimates will be provided where appropriate. Treatment difference along with 95% CI will also be reported for Part 2 of the study. Subgroup analysis by stratification factors, i.e. age (<60 year vs. ≥60 years) and use of remdesivir (yes vs. no) might be performed where data permits.

For the efficacy endpoints in Part 2, the primary endpoint will be analyzed using the exact method. Difference between two arms will be tested by a stratified Cochran–Mantel–Haenszel test (CMH) test using the stratification factors at randomization. Recovery rate by Day 14, recovery rate by Day 30, and all-cause mortality rate will be analyzed similarly. Time to recovery among subjects alive by Day 30 will be analyzed by a stratified log-rank test for p-

value, and the HR ratio between two arms will be estimated by a stratified Cox proportional hazard model using the stratification factors at randomization. For the phase 2 portion the primary analysis will be based on the ITT population. For the phase 3 portion the primary analysis will be based on the mITT population, and sensititivy analyses will be conducted based on the ITT population.

For the Part 2 phase 3 portion, multiplicity will be adjusted by a gatekeeping procedure. If the null hypothesis for the primary endpoint is rejected, then the key secondary endpoints will be tested in the order of: proportion of recovered subjects by Day 14, proportion of recovered subjects by Day 30, and all-cause mortality rate by Day 30.

The primary clinical question of interest for the primary objective is whether there is a difference in proportion of subjects who are alive and free of mechanical ventilation after 30 days comparing TJ003234 10 mg/kg versus placebo in COVID-19 subjects who have low blood oxygen or requires high flow oxygen regardless of initiation of additional medication or change in background medication (remdesivir and/or steroids). The clinical question of interest for the secondary objectives are similar, which is whether there is a difference in proportion of subjects who will recover after 14 or 30 days comparing TJ003234 10 mg/kg versus placebo in iCOVID-19 subjects who have low blood oxygen or requires high flow oxygen regardless of initiation of additional medication or change in background medication (remdesivir and/or steroids).

The estimand is described by the following attributes:

- Population: severe hospitalized COVID-19 subjects who require non mv oxygen supply at baseline.
- Endpoint: proportion of subjects who are non-mechanical ventilated at baseline by Day 30.
- Treatment condition: TJ003234 10 mg/kg and placebo with or without background medication (remdesivir and/or steroids).
- Intercurrent events and strategies: The intercurrent events “change in background medication (remdesivir and/or steroids)” are addressed by the treatment condition of interest attribute following the treatment policy strategy. Other relevant intercurrent events are not anticipated at this point in time.
- Population-level summary: difference in proportions between treatment conditions

The trial will be considered as successful if the primary endpoint in Phase 3 portion shows a statistically significant improvement in the treatment arm and, as a safety measurement, the all-cause mortality rate in the treatment arm is numerically not higher than that in the control arm.Sensitivity analyses and subgroup analysis will be performed to investigate the robustness of the primary efficacy outcome. Details will be provided in the statistical analysis plan (SAP).

9.6. Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is responsible for monitoring safety. The IDMC will be made up entirely of members external to I-Mab. The IDMC charter will contain membership information and a further delineation of responsibilities.

The IDMC may recommend continuing enrollment in one dose arm or to terminate the study for accumulated safety evaluations. The IDMC will provide a recommendation that is made without known bias. I-Mab staff involved in the conduct of the study will be kept blinded to before a portion of the study is completed, and the members of the IDMC will not have involvement with the conduct of the study.

10. Regulatory Human Subject Protection and Regulatory Oversight

10.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB) by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.2. Informed Consent Processes and Documentation

In obtaining and documenting informed consent, the Investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the Investigator should have the IRB's written approval for the protocol and the written ICF and any other written information to be provided to the participants. Participants will be asked to read and review the IRB-approved ICF and other written information. The ICF should include a detailed description of study procedures, risk and benefits, directions, participant's rights, compensation (if applicable), and

contact of Human Subject Protection Services. Additionally, the Investigator will explain the research study to the participant in terms suited to the participant's comprehension and answer any questions that may arise. The Investigator should explain their rights as research participants, study procedures, risk and benefits, and anticipated adverse effects. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. ICF should be signed prior to any interventions are performed for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Participant will be given a copy of the signed consent form and the original consent form will be kept as a permanent record.

10.3. Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating Investigator(s), their staff, and the Sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or Sponsor requirements.

Research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the data management group at the designated CRO. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by CRO staff will be secured, and password protected. At the end of the study, all study databases will be de-identified and archived at the CRO or Sponsor until further data integration with future studies of TJ003234.

10.4. Conflict of Interest

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the

design and conduct of this trial.

11. Quality Control and Quality Assurance

Sponsor or designee will conduct periodic monitoring visits to ensure that the protocol and current Good Clinical Practices within standard operating procedures are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The Investigator and institution will allow the Sponsor's medical monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the electronic CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria, and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study specific monitoring plan.

12. Confidentiality and Publication of Test Results

All information about this trial (including but not limited to the following documents: protocols, investigator's brochure) must be kept strictly confidential. Investigators shall be aware that the scientific or medical information derived from this trial may be of commercial value to the sponsor. Investigators should keep the information and data related to the trial confidential. If Investigators are intended to publicly release information or conclusions obtained from the trial, they shall consult with the sponsor in advance and obtain the written consent of the sponsor. In order to protect rights and interest, the sponsor may require investigators not to publish information about the trial until the trial product is approved for marketing.

The sponsor has the right to publish or release information or data related to the trial, or report them to the regulatory authorities.

13. References

Avci, A.B., Feist, E. and Burmester, G.R. (2016). Targeting GM-CSF in Rheumatoid Arthritis. C*lin Exp Rheumatol*, 34 (4 Suppl 98):39–44.

Beigel, J.H., Tomashek, K.M., Dodd, L.E., Mehta, A.K., Zingman, B.S., Kalil, A.C.,… Lane, H.C. for the ACTT-1 Study Group Members (2020). Remdesivir for the Treatment of Covid-19 — Preliminary Report. *New England Journal of Medicine*, Published Online 2020 May 22; NEJMoa2007764. doi: 10.1056/NEJMoa2007764.

Broughton, S. E., Nero, T. L., Dhagat, U., Kan, W. L., Hercus, T. R., Tvorogov, D., … Parker, M. W. (2015). The βc receptor family – Structural insights and their functional implications. *Cytokine*, *74*(2), 247–258. doi: 10.1016/j.cyto.2015.02.005

Burmester, G. R., Mcinnes, I. B., Kremer, J., Miranda, P., Korkosz, M., Vencovsky, J., … Weinblatt, M. E. (2017). A randomised phase IIb study of mavrilimumab, a novel GM–CSF receptor alpha monoclonal antibody, in the treatment of rheumatoid arthritis. *Annals of the Rheumatic Diseases*, *76*(6), 1020–1030. doi: 10.1136/annrheumdis-2016-210624

Channappanavar, Rudragouda, and Stanley Perlman. "Pathogenic Human Coronavirus Infections: Causes and Consequences of Cytokine Storm and Immunopathology." *Seminars in Immunopathology*, vol. 39, no. 5, Feb. 2017, pp. 529–539., doi:10.1007/s00281-017-0629-x.

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., … Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*, *395*(10223), 507–513. doi: 10.1016/s0140-6736(20)30211-7

Chinese Clinical Trial Registry. (n.d.). Retrieved from http://www.chictr.org.cn/showproj.aspx?proj=49409

De Luca, G., Cavalli, C., Campochiaro, C., Della-Torre, E., Angelillo, P., Tomelleri, A.,… Dagna. L. (2020). GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study. *Lancet Rheumatol*, Published Online June 16, 2020 doi: https://doi.org/10.1016/S2665-9913(20)30170-3

FDA Guidance for Industry. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005

Gilead. Press Releases. https://www.gilead.com/news-and-press/press-room/press-releases. Accessed March 8, 2020.

Goldman, J.D., Lye, D.C.B., Hui, D.S., Marks, K.M., Bruno, R., Montejano, R, … and

Subramanian, A. (2020). Remdesivir for 5 or 10 Days in Patients with Severe Covid-19 *New England Journal of Medicine*, Published Online May 27, 2020, DOI: 10.1056/NEJMoa2015301

Guan, W.-J., Ni, Z.-Y., Hu, Y., Liang, W.-H., Ou, C.-Q., He, J.-X., … Zhong, N.-S. (2020). Clinical characteristics of 2019 novel coronavirus infection in China. doi: 10.1101/2020.02.06.20020974

Gust J, Finney O, Li D, Brakke HM, Hicks RM et al. (2019). Glial injury in neurotoxicity after pediatric CD19-directed chimeric antigen receptor T cell therapy. *Ann Neurol*. 86(1):42-54.

Hamilton, J. A. (1980). Macrophage stimulation and the inflammatory response to asbestos. *Environmental Health Perspectives*, *34*, 69–74. doi: 10.1289/ehp.803469

Hansen, G., Hercus, T., Woodcock, J., Mcclure, B., Stomski, F., Xu, Y., … Parker, M. (2008). Structure of the GM-CSF Receptor Complex. doi: 10.2210/pdb3cxe/pdb

Hercus, T. R., Kan, W. L. T., Broughton, S. E., Tvorogov, D., Ramshaw, H. S., Sandow, J. J., … Lopez, A. F. (2017). Role of the β Common (βc) Family of Cytokines in Health and Disease. *Cold Spring Harbor Perspectives in Biology*, *10*(6). doi: 10.1101/cshperspect.a028514

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, *395*(10223), 497–506. doi: 10.1016/s0140-6736(20)30183-5

Huizinga, T. W. J., Batalov, A., Stoilov, R., Lloyd, E., Wagner, T., Saurigny, D., … Esfandiari, E. (2017). Phase 1b randomized, double-blind study of namilumab, an anti-granulocyte macrophage colony-stimulating factor monoclonal antibody, in mild-to-moderate rheumatoid arthritis. *Arthritis Research & Therapy, 19*(1). doi: 10.1186/s13075-017-1267-3

I-Mab Biopharma. TJ003234RAR101 Clinical Study Report. (Version 1.0). 03 January 2020.

I-Mab Biopharma. TJ003234 – Investigator's Brochure. (Version 3.0). XX March 2020.

Jenkins, B. J., Blake, T. J., & Gonda, T. J. (1998). Saturation Mutagenesis of the β Subunit of the Human Granulocyte-Macrophage Colony-Stimulating Factor Receptor Shows Clustering of Constitutive Mutations, Activation of ERK MAP Kinase and STAT Pathways, and Differential β Subunit Tyrosine Phosphorylation. *Blood*, *92*(6), 1989–2002. doi: 10.1182/blood.v92.6.1989.418k18_1989_2002

Lang, F.M., Lee, K. M.-C., Teijaro, J.R., Becher, B., & Hamilton J. A. (2020). GM-CSF-

based treatments in COVID-19: reconciling opposing therapeutic approaches. *Nat Rev Immunol*. *2020 Jun 23;*1-8. doi: 10.1038/s41577-020-0357-7.

Le, R. Q., Li, L., Yuan, W., Shord, S. S., Nie, L., Habtemariam, B. A., … Przepiorka, D. (2018). Tocilizumab for Treatment of Severe or Life-Threatening Chimeric Antigen Receptor T Cell-Induced Cytokine Release Syndrome—FDA Approval Summary. *Biology of Blood and Marrow Transplantation*, *24*(3). doi: 10.1016/j.bbmt.2017.12.104

Ryan, P. C., Sleeman, M. A., Rebelatto, M., Wang, B., Lu, H., Chen, X., … Dixit, R. (2014). Nonclinical safety of mavrilimumab, an anti-GMCSF receptor alpha monoclonal antibody, in cynomolgus monkeys: Relevance for human safety. *Toxicology and Applied Pharmacology*, *279*(2), 230–239. doi: 10.1016/j.taap.2014.06.002

Sachdeva, Mohit, et al. "Granulocyte–Macrophage Colony-Stimulating Factor Inactivation in CAR T-Cells Prevents Monocyte-Dependent Release of Key Cytokine Release Syndrome Mediators." *Journal of Biological Chemistry*, vol. 294, no. 14, 2019, pp. 5430–5437., doi:10.1074/jbc.ac119.007558.

Sato, N., Sakamaki, K., Terada, N., Arai, K., & Miyajima, A. (1993). Signal transduction by the high-affinity GM-CSF receptor: two distinct cytoplasmic regions of the common beta subunit responsible for different signaling. *The EMBO Journal*, *12*(11), 4181–4189. doi: 10.1002/j.1460-2075.1993.tb06102.x

Schulert, Grant S., et al. "Systemic Juvenile Idiopathic Arthritis–Associated Lung Disease: Characterization and Risk Factors." *Arthritis & Rheumatology*, vol. 71, no. 11, 2019, pp. 1943–1954., doi:10.1002/art.41073.

Sterner, RM, et al. GM-CSF inhibition reduces cytokine release syndrome and neuroinflammation but enhances CAR-T cell function in xenografts. *Blood*. 2019;133(7):697-709

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., … Peng, Z. (2020). Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *Jama*. doi: 10.1001/jama.2020.1585

Xu Z, Shi L, Wang Y, Zhang J, Huang J, et al. (2020). Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. doi: 10.1016/S2213-2600(20)30076-X.

Zhou, Yonggang, et al. "Aberrant Pathogenic GM-CSF T Cells and Inflammatory CD14 CD16 Monocytes in Severe Pulmonary Syndrome Patients of a New Coronavirus." 2020, doi:10.1101/2020.02.12.945576.

14. Appendices

14.1. Appendix 1: Contraceptive requirements

Definition of women of childbearing potential:

Non-fertile women are defined as post-menopausal women and pre-menopausal women who have undergone surgical sterilization. Postmenopausal is defined as menopause ≥ 12 months without alternative medical measures. Follicle Stimulating Hormone (FSH) test should be performed for subjects who are not sure of their menopausal status, and if FSH>40 MlU/mL, it can be confirmed as menopause. Sterilization operations include bilateral fallopian tube ligation or bilateral ovariectomy or hysterectomy.

Women of childbearing age are defined as those who are anatomically and physiologically able to get pregnant.

Contraceptive requirements

Women of childbearing potential must have a negative pregnancy test during the screening period. If of childbearing potential, women must agree to one of the following methods of contraception beginning at screening and continuing for a period of 4 months after the final dose of IP:

- Hormonal contraception (e.g., oral contraceptive, contraceptive implant, or injectable hormonal contraceptive)
- Double-barrier birth control (e.g., condom plus intrauterine device, diaphragm plus spermicide or condom plus spermicide)
- Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy
- Abstinence

Male subjects who are sexually active must agree to use a double-barrier method of contraception (condom with spermicide) from the first dose of randomized study drug until 4 months after their last dose and must not donate sperm during their study participation period.

14.2. Appendix 2: Cardiac Function Grading of NYHA

Grade I: A patient has a heart disease, but his/her daily activity is not limited. General physical activity will not cause excessive fatigue, palpitations, asthma or angina.

Grade II: a patient with heart disease has slightly limited physical activity. He/she has no conscious symptoms at rest, and general physical activity may cause excessive fatigue, palpitations, asthma or angina.

Grade III: a patient with heart disease has obviously limited physical activity. He/she has no symptoms at rest, but physical activity lower than normal level may cause excessive fatigue, palpitations, asthma or angina.

Grade IV: a patient with heart disease cannot engage in any physical activity, and heart failure symptoms also occur during rest, which worsens after physical activities.

14.3. Appendix 3: Sequential Organ Failure Assessment Score

System	Test Item	0	1	2	3	4	Score
Respiratory system	PaO2/FiO2, mmHg (kPa)	>400 (>53.33)	301-400 (≤53.33 and >40)	201-300 (≤40 and >26.67)	101-200 (≤26.67)	≤100 (<13.33)	
	Respiratory support (yes/no)				Yes	Yes	
Coagulation system	Platelets, 10^9/L	>150	101-150	51-100	21-50	<21	
Liver	Bilirubin, mg/dL (umol/L)	<1.2 (<20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (>204)	
Circulatory system	Mean arterial pressure (mmHg)	≥70	<70				
	Dopamine dose (ug/kg/min)			≤5 or	>5 or	>15 or	
	Adrenaline dose (ug/kg/min)				≤0.1 or	>0.1 or	
	Norepinephrine dose (ug/kg/min)				≤0.1	>0.1	
	Dobutamine (yes / no)			Yes			
Nervous system	GCS score	15	13-14	10-12	6-9	<6	
Kidneys	Creatinine, mg/dL (umol/L)	<1.2 (<110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (>440)	
	24-hour urine output (ml/24h)				201-500	<200	
Remarks:	1. The worst daily value should be taken for daily assessment; 2. The higher the score, the worse the prognosis.						

	3. For the respiratory system score, to receive a score of 3 or 4 points, the patient needs to be mechanically ventilated. If the patient has a PaO2/FiO2 value of ≤40 kPa and the patient is not on mechanical ventilation, the score will be 2, regardless if the value is lower than 26.67.

14.4. Appendix 4: Inhaled corticosteroid dose guidance

Adapted from Global Strategy for Asthma Management and Prevention – GINA 2019.
This is not a table of equivalence, but of estimated clinical comparability based on available studies and product information.
Doses are in mcg. CFC: chlorofluorocarbon propellant. DPI: dry powder inhaler. HFA: hydrofluoroalkane propellant.

Inhaled corticosteroid	**Adults and adolescents**		
	Low	**Medium**	**High**
Beclometasone dipropionate (CFC)	200-500	>500-1000	>1000
Beclometasone dipropionat	100-200	>200-400	>400
Budesonide (DPI)	200-400	>200-400	>400
Ciclesonide (HFA)	80-160	>160-320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone priopionate (DPI)	100-250	>250-500	>500
Fluticasone priopionate (HFA)	100-250	>250-500	>500
Mometasone furoate	110-220	>220-440	>440
Triamcinolone acetonide	400-1000	>1000-2000	>2000

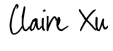
DocuSign

Certificate Of Completion

Envelope Id: 00A93AB15C5E45AE8208C5DCDBA11A37
Status: Completed
Subject: Please DocuSign: TJ003234COV201_Protocol_Version 9.0_FINAL_23Sep2021.docx
Source Envelope:
Document Pages: 80
Signatures: 1
Envelope Originator:
Certificate Pages: 4
Initials: 0
Andria White
AutoNav: Enabled
Andria.White@i-mabbiopharma.us
EnvelopeId Stamping: Disabled
IP Address: 24.47.35.145
Time Zone: (UTC+08:00) Beijing, Chongqing, Hong Kong, Urumqi

Record Tracking

Status: Original
9/24/2021 3:38:54 AM
Holder: Andria White
Andria.White@i-mabbiopharma.us
Location: DocuSign

Signer Events	Signature	Timestamp
Claire Xu claire.xu@i-mabbiopharma.com US Site Head Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 694B2B1E-EED8-462B-8E8C-4CD8F1AD4794 Using IP Address: 71.246.231.35 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 9/24/2021 3:39:58 AM Viewed: 9/24/2021 3:48:18 AM Signed: 9/24/2021 3:48:32 AM
Electronic Record and Signature Disclosure: Accepted: 9/24/2021 3:48:18 AM ID: 1ddbbfe1-06b7-494b-ba6f-d5cffbdcc3c2		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	9/24/2021 3:39:58 AM
Certified Delivered	Security Checked	9/24/2021 3:48:18 AM
Signing Complete	Security Checked	9/24/2021 3:48:32 AM
Completed	Security Checked	9/24/2021 3:48:32 AM
Payment Events	**Status**	**Timestamps**

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Ingram Micro (China) Limited OBO Master Concept OBO I-MAB Biopharma Co Ltd (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Ingram Micro (China) Limited OBO Master Concept OBO I-MAB Biopharma Co Ltd:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: wink.lv@i-mabbiopharma.com

To advise Ingram Micro (China) Limited OBO Master Concept OBO I-MAB Biopharma Co Ltd of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at wink.lv@i-mabbiopharma.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Ingram Micro (China) Limited OBO Master Concept OBO I-MAB Biopharma Co Ltd

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to wink.lv@i-mabbiopharma.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Ingram Micro (China) Limited OBO Master Concept OBO I-MAB Biopharma Co Ltd

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to wink.lv@i-mabbiopharma.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Ingram Micro (China) Limited OBO Master Concept OBO I-MAB Biopharma Co Ltd as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Ingram Micro (China) Limited OBO Master Concept OBO I-MAB Biopharma Co Ltd during the course of your relationship with Ingram Micro (China) Limited OBO Master Concept OBO I-MAB Biopharma Co Ltd.