DRUG:	INM005
STUDY NUMBER(S):	CT-INM005-01
PROTOCOL TITLE:	A phase II/III, adaptive, randomised, controlled, double-blind study to investigate the pharmacokinetics, efficacy and safety of the hyperimmune equine serum INM005 in adult patients with moderate to severe confirmed SARS-CoV-2 disease.
SPONSOR:	INMUNOVA S.A. 25 de Mayo 1021 (ZC 1650), San Martín, Buenos Aires, Argentina.
DATE OF ORIGINAL PROTOCOL:	05-Jul-2020
VERSION NUMBER:	1.1 ADMINISTRATIVE AMENDMENT
VERSION DATE:	28SEP2020

CLINICAL PROTOCOL APPROVAL FORM

Protocol title: A phase II/III, adaptive, randomised, controlled, double-blind study to investigate the pharmacokinetics, efficacy and safety of the hyperimmune equine serum INM005 in adult patients with moderate to severe confirmed SARS-CoV-2 disease.

Study No.: CT-INM005-01

Date of original protocol: 5-Jul-2020

Protocol version No.: 1.1 ADMINISTRATIVE AMENDMENT

Protocol version date.: 28SEP2020

This study protocol has been critically reviewed and approved by the sponsor's Protocol Review Committee. The information contained in this protocol is consistent with:

- The current benefit-risk assessment of the investigational medicinal product (IMP) (i.e., INM005).
- The moral, ethical and scientific principles that govern clinical research as established in the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) and the applicable local requirements.

The investigator will be informed of any new or significant findings, including adverse events (AE), related to the treatment with INM005.

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INVESTIGATOR STATEMENT OF CONFIDENTIALITY AND COMMITMENT

A PHASE 2/3, ADAPTIVE, RANDOMISED, CONTROLLED, DOUBLE-BLIND STUDY TO INVESTIGATE THE PHARMACOKINETICS, EFFICACY AND SAFETY OF THE HYPERIMMUNE EQUINE SERUM INM005 IN ADULT PATIENTS WITH MODERATE TO SEVERE CONFIRMED SARS-CoV-2 DISEASE.

The information contained in this protocol and all other relevant information in relation to INM005 constitutes confidential information owned by INMUNOVA S.A., and may not be disclosed to third parties without prior written authorisation from INMUNOVA SA, unless required by local, state or federal laws or regulations.

I agree to provide all study staff under my supervision with copies of the protocol and its amendments, as well as access to all the information provided by INMUNOVA or the persons designated to that end. I will also review this material with the staff members to ensure they are fully informed about INMUNOVA and this study.

By signing below, I confirm that I have read this protocol and consider that it contains all the information necessary to carry out the study. I confirm that I will carry out the study in accordance with the provisions of current local regulations on the matter and the guidelines of the International Council on Harmonisation of Technical Requirements for the Registration of Pharmaceutical Products for Human Use that have their origin in the Declaration of Helsinki, and in accordance with the procedures described in this protocol.

Name of the Principal Investigator (printed)	Signature
Date	Site number

CHANGES IN THE AMENDMENT CT-INM005-01

Below is the summary of the changes included in this administrative amendment to the Protocol:

Section 5.2 and 11.7
The cut-off value of the interim analysis is modified: it will be carried out when the follow-up of approximately 145 patients (60% recruitment) is completed instead of 192 patients (80% recruitment).

The changes notified in due time in the **ERRATUM v1.0_7ago2020** are also incorporated:

- **MANAGEMENT OF THE STUDY DRUG**

By mistake, on page 97, it was stated, "Each vial contains 25 mg of protein/ml", but it should read, "Each ml contains 30 mg of protein," as stated in Table 8.1, on page 96.

By mistake, on page 97, it was stated, “Each vial contains 25 mg of protein/ml, therefore each subject should receive 0.16 ml/kg”. The statement should read, "Each vial contains 30 mg of protein/ml, therefore each subject must receive 0.13 ml/kg," as established in the INVESTIGATIONAL PRODUCT HANDLING MANUAL: INM005 (v1.0 of 15Jul2020).

By mistake, on page, 97 it was stated, "Two doses of IMP will be administered as an infusion at a rate of 2.0 ml/min over a 50 min period with a 24 h interval between doses." It should read, “Two doses of IMP will be administered as an infusion at a rate of 2.0 ml/min over a 50-minute period with a 48-hour interval between doses” as stated in section 1.4.

- **PHARMACOKINETICS**

In the study schedule, on page 73, an “X” appears on day 5 for the item “Extraction of PK samples (pharmacokinetics)”, but it should appear on day 7 as established in section 1.4.6, and in the footer of the schedule (item 24).

The changes notified in due time in the **CLARIFICATION LETTER v1.0_19ago2020** are also incorporated:

- **SECTION 1.1.1.3 Stratification by Risk - DEFINITION OF MODERATE CASE OF COVID-19**

It is hereby clarified that the definition used in the reference protocol is that cited by the US National Institute of Health (NIH) according to what is mentioned on protocol page 32 (quote 36):
https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/:

Moderate disease: Individuals who have evidence of lower respiratory disease, as assessed by clinical evaluation or imaging and an oxygen saturation (SpO2) ≥ 94% in ambient air.

By mistake, a preliminary definition was left in the protocol that does not coincide with quote 36: (Patients with fever, respiratory symptoms and radiological findings of pneumonia)

- **SECTION 7.1 Efficacy Assessments - WHO ORDINAL SCALE**

Patient classification according to the WHO scale is based on the quote "WHO R&D Blueprint Novel Coronavirus," as stated in the protocol, on page 88 (quote 78): https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf

By mistake, the inclusion for scale 4 that the requirement for oxygen can be by means of a mask or nasal tube, was omitted
0- No evidence of infection
1- Outpatient, with no limitation to activities
2- Outpatient, with limitation to activities
3- Hospitalised with no oxygen therapy requirement
4- Oxygen therapy employing either a mask or a nasal tube
5- Non-invasive ventilation or high-flow oxygen
6- Intubation and mechanical ventilation
7- Mechanical ventilation and organ support (vasopressors, ECMO [extracorporeal membrane oxygenation], RRT [renal replacement therapy])
8- Death

- **5.3 Inclusion/Exclusion Criteria - EXAMPLES OF PRIOR USE OF EQUINE SERUM IN HISTORY**

In relation to the examples proposed for the assessment of the exclusion criterion 4: 4. History of anaphylaxis, previous administration of equine serum (e.g. anti-tetanus serum or antivenin serum, or arachnid antitoxin serum), or an allergic reaction by contact or exposure to horses", it is clarified that the production of equine anti-tetanus serum stopped in 1970, and therefore a patient to whom the anti-serum was administered after that date may be a candidate for the study, for the serum is of human origin.

- **10.2 NOTIFICATION OF SERIOUS ADVERSE EVENTS (SAEs)**

It is clarified that, for the reference study, the events that the investigator considers to be related to COVID-19 progression are part of the primary and secondary data set used for the study efficacy analyses, and therefore will not be considered as an AE, will not be registered

as a SAE in the clinical study safety database, and will not be notified to regulatory authorities under expedited modality.

Regarding death events, in all cases they should be reported as an SAE as described in Section 10.1 of the protocol.

STUDY SUMMARY

Title:	**A phase 2/3, adaptive, randomised, controlled, double-blind study to investigate the pharmacokinetics, efficacy and safety of the hyperimmune equine serum INM005 in adult patients with moderate to severe confirmed SARS-CoV-2 disease.**
Clinical Phase:	**2/3**
Rationale:	**The pandemic caused by the novel coronavirus has generated an unprecedented situation in recent history, with several million infected and hundreds of thousands of deaths. This disease is easily transmissible by air. Although a high percentage of patients have a mild clinical presentation, approximately 15% of them present a moderate to severe disease, and 5% require intensive care with mechanical ventilation and face a high risk of mortality. No effective therapies for the treatment or prevention of SARS-CoV-2 have been identified so far. Preliminary evidence indicates that passive immunotherapy with convalescent plasma could favourably alter the clinical course of this infection. This strategy, even if confirmed as successful, requires voluntary donation by patients who have recovered, not all of whom are eligible as donors, since the antibody response magnitude varies among different patients. This study aims at studying the efficacy and safety of passive immunotherapy by administering hyperimmune serum INM005 generated by the antigenic stimulation of equines. INM005 is a product that is biologically equivalent to the anti-Shiga toxin serum that neutralises the interaction of SARS-CoV-2 with its cellular receptor, thus preventing virus multiplication. The safety information for the anti-Shiga toxin serum indicates that it is well tolerated and that no serious adverse events or suspensions of treatment have been reported. The objective of this adaptive Phase 2/3 study is to demonstrate the safety and efficacy of INM005 to improve the clinical course of COVID-19 28 days after the start of treatment with the investigational product, in individuals with moderate to severe disease requiring hospitalisation.**
Target Population:	**Patients with moderate or severe COVID-19 as defined by NIH, requiring hospitalisation, excluding patients with either mechanical ventilation or admission to ICU.**
Number of Participants:	**242 patients / approximately 10 sites**

Objectives and Endpoints:

Primary objective

To demonstrate the efficacy and safety of INM005 in COVID-19 in terms of clinical improvement 28 days after the start of treatment with the investigational product.

Primary efficacy endpoint:

The proportion of patients that showed improvement 28 days after the administration of the first dose will be determined. A responder subject is defined as a subject with an improvement in at least 2 categories in the 8-point WHO clinical status ordinal scale, or with hospital discharge.

Safety endpoints:

Incidence of related adverse events and of adverse events of special interest during the study period

Secondary objectives

1) Assessment of the pharmacokinetics of INM005

2) Assessment of efficacy in terms of time to disease progression

3) Assessment of efficacy in terms of disease progression

4) Assessment of efficacy in terms of change in viral load

Secondary endpoints:

1) Concentration of product INM005 in serum at different times after administration of treatment

2) Time to improvement in at least 2 categories in the 8-point WHO clinical status ordinal scale

Time to discharge (days)

Time to discharge from ICU (days)

3) Proportion of patients who show an improvement in at least 2 categories in the 8-point WHO clinical status ordinal scale 7 and 14 days after the start of the treatment

Proportion of patients with hospital discharge at 28 days

Proportion of patients who required admission to ICU

Proportion of patients who required MV

Proportion of patients who died

4) Changes in viral load from baseline to 7 days and 21 days after the start of treatment

<u>Exploratory objectives:</u>

1) Assessment of anti-SARS-CoV-2 antibodies levels

2) Assessment of changes in laboratory variable predictors of disease progression

3) Assessment of immunogenicity at 28 days

<u>Exploratory endpoints:</u>

1) Measurement of anti- SARS-CoV-2 antibody titres: IgG (0, 21 days)

2) Measurable laboratory variables at baseline, 7 and 21 days: troponin T, D-dimer, ferritin, LDH, C-reactive protein

3) Measurement of anti-INM005 product antibodies: baseline and 21 days

Study Design: **Randomised, double-blind, parallel group study with adaptive design. The interim analysis will be performed in a "blinded" manner and, based on the rate of events in the control group, the futility of the treatment, the feasibility of the study, or the sample size will be adapted.**

Randomisation:	**1:1 (INM005: placebo)** **A staggered enrolment of the first 12 subjects will be performed in 6:6 blocks. Randomisation will be carried out maintaining a 1:1 ratio in each sub-cohort:** • **active treatment regime [2 4-mg/kg doses of INM005]** • **placebo**

Study Visits: **Visit 1 - Screening Day 0**

After confirmation of COVID-19 diagnosis by PCR, the following procedures will be conducted

– Explanation and signature of the informed consent

- Demographics:

- **Age**
- **Sex**
- **Ethnicity**

- Clinical History:

• Relevant Medical History

• Underlying Diseases:

o any cardiovascular disease

o any chronic pulmonary disease

o kidney disease

o diabetes

o liver disease

o immunodeficiencies

o neurological disability

o others

• Allergies to medications and/or horses

• Any medical condition that after signing the informed consent should be informed as an adverse event (AE)

- History of the Disease:

• date of the first symptom

• source of infection

• symptoms according to the definition of case by the Ministry of Health of Argentina

- Patient classification according to the 8-point WHO scale

- Physical Exam

- Vital Signs

• Heart rate

• Respiratory rate

• Oxygen saturation percentage/FiO2 saturation

• Blood pressure

• Temperature

- Laboratory tests and imaging

• Haematology

• Full chemical panel (including LDH)

• Chest X-ray

- Inclusion/Exclusion criteria

Visit 2 - Baseline - Day 1 (within 24 hours after screening visit)

- Physical exam and laboratory tests, if more than 24 hours have elapsed

- Assessment of COVID-19 symptoms

- Patient classification according to the WHO Scale

- Confirmation of eligibility

- Randomisation

- Preparation of the infusion by the unblinded staff

- Vital signs 15 minutes prior to infusion

- For PK sub-study: pre-infusion blood sample for the pharmacokinetics study

- Blood samples for viral load (central laboratory)

- Blood samples for anti-SARS-CoV-2 antibodies, biomarkers and immunogenicity (central laboratory)

- Administration of double-blind treatment: 100 ml infusion over 50 minutes

Post-treatment administration procedure:

- For PK sub-study: Sample tests for pharmacokinetics (5 minutes after the end of infusion)

- Assessment of hypersensitivity reactions within 15 minutes post-infusion

- Assessment of adverse events and concomitant medication

- Vital signs within 15 minutes post-infusion

Visit 2 - Day 2 (1st. dose follow-up)

- Safety laboratory tests 24 h post-infusion

- **Haematology**
- **Full chemical panel**

– Vital signs

- Patient classification according to the WHO scale

- Assessment of hypersensitivity reactions

- Assessment of adverse events and concomitant medication

- Assessment of COVID-19 disease and complications

Visit 3 - Day 3 (second dose of treatment)

- Preparation of the infusion by the unblinded staff

- Assessment of adverse events and concomitant medication

- Patient classification according to the WHO scale

- Assessment of COVID-19 disease and complications

- Vital signs 15 min prior to infusion

- For PK sub-study: Pre-infusion blood sample for the pharmacokinetics

- Administration of double-blind treatment: 100 ml infusion over 50 minutes

Post-treatment administration procedure:

- For PK sub-study: Samples for pharmacokinetics (5 minutes after the end of infusion)

- Assessment of hypersensitivity reactions within 15 minutes post-infusion

- Assessment of adverse events and concomitant medication

- Vital signs within 15 minutes post-infusion

Visit 3 - Day 4 (2nd. dose follow-up)

- For PK sub-study: Samples for pharmacokinetics (24 h post second infusion)

- Safety laboratory tests, 24 h post-infusion

- **Haematology**
- **Full chemical panel**

- Vital signs

- Patient classification according to the WHO scale

- Assessment of hypersensitivity reactions

- Assessment of adverse events and concomitant medication

- Assessment of COVID-19 disease and complications

– Hospital discharge if the patient is clinically stable and with medical criteria for discharge

Visit 4- Day 5 (follow-up)

- Vital signs

- Patient classification according to the WHO scale

- Assessment of COVID-19 disease and complications

- Assessment of hypersensitivity reactions

- Assessment of adverse events and concomitant medication

Visit 5- Day 7 (follow-up)

- Vital signs

- Patient classification according to the WHO scale

- Assessment of COVID-19 disease and complications

- Assessment of hypersensitivity reactions

- Assessment of adverse events and concomitant medication

- Obtention of samples for viral load

- Obtention of blood samples for anti-SARS-CoV-2 antibodies and laboratory markers

- Only for PK sub-study: Obtention of blood sample for the pharmacokinetics study

Visit 6- Day 14 (follow-up)

- Vital signs

- Patient classification according to the WHO scale

- Assessment of COVID-19 disease and complications

- Assessment of hypersensitivity reactions

- Assessment of adverse events and concomitant medication

Visit 7- Day 21 (follow-up)

- Vital signs

- Patient classification according to the WHO scale

- Assessment of COVID-19 disease and complications

- Assessment of hypersensitivity reactions

- Assessment of adverse events and concomitant medication

- Samples for viral load

- Blood samples for anti-SARS-CoV-2 antibodies and laboratory markers, immunogenicity

– Safety laboratory tests

- **Haematology**
- **Full chemical panel**

Visit 8- Day 28 (End of study)

- Vital signs

- Patient classification according to the WHO scale

- Assessment of COVID-19 disease and complications

- Assessment of hypersensitivity reactions

- Assessment of adverse events and concomitant medication

- Assessment of adverse events and concomitant medication

Eligibility criteria:

Inclusion criteria

Subjects must meet all the inclusion criteria at Screening:

1. **Both sexes, aged 18 to 79 years of age**
2. **SARS-CoV-2 infection confirmed by PCR**
3. **Moderate or severe disease according to NIH definition, requiring hospitalisation**
4. **Acceptance of participation in the study by signature of informed consent (by subject or relative, if applicable)**

5. **To be within 10 days of the onset of symptoms at the time of the Screening visit, according to a case definition from the National Ministry of Health**
6. **Female patients at child-bearing age with negative pregnancy test**

Exclusion criteria

Subjects must not meet any of the following exclusion criteria at the time of Screening:

1. **Patients who have received treatment with plasma from COVID-19 convalescents**
2. **Patients who are participating in other therapeutic clinical trials**
3. **Patients who require mechanical ventilation or who are hospitalised in the ICU at the screening visit**
4. **History of anaphylaxis, prior administration of equine serum (for example, anti-tetanus serum or anti-ophidic serum or anti-arachnid toxin serum) or allergic reaction due to contact or exposure to horses**
5. **Pregnant or breastfeeding women**
6. **Patients who, at the doctor's judgement, within the next 30 days due to a concomitant disease other than the study disease**
7. **Patients who are expected to be referred to another institution within 72 hours of enrolment, which prevents adequate follow-up of that patient**

Study drug:

The INM005 treatment scheme is based on a history of INM004 (hyperimmune equine anti-Shiga toxin serum). The maximum dose tested in Phase I of INM004 was 4 mg/kg and up to 3 doses spaced 24 apart.

Each dose is administered as an intravenous infusion (i.v.) over a period of 50 min with an interval of 48 h (± 2 h) with each other.

The proposed treatment scheme is as follows:

- **2 doses of INM005, 4 mg/kg, or**
- **2 doses of placebo**

Safety evaluations

Vital signs

Laboratory evaluations

AE and serious adverse events (SAEs)

AESI:

o Injection site reaction

	o Hypersensitivity reactions (i.e. allergic reaction, anaphylaxis and serum sickness)
Data monitoring committee	**A DMC will be formed to evaluate the Safety of the study periodically when the first 12, 24, 48, 96 and 192 patients have been recruited. A data review will be done during the interim analysis when approximately 145 patients have been recruited.** **A staggered recruitment of the first 12 subjects will be performed in 6:6 blocks. Randomisation will be carried out maintaining a 1:1 ratio in each sub-cohort:** **• Active treatment regime [two 4-mg/kg doses of INM005]** **• Placebo** **Intensive monitoring will be done during this stage.** **After the first 6 subjects have been recruited and 24hours post treatment have passed after the second dose, the Sponsor's Medical Monitor will review the safety data for this acute phase and report the safety findings.** **This evaluation will be repeated for the 2 blocks of 6 subjects each.** **Any safety findings will be notified immediately to the Sponsor, DMC and Regulatory Agency, as established in current regulations.** **The monitoring details will be specified in the Study Pharmacovigilance Plan, which will be finalised before the recruitment of the first patient into the study begins.** **When the recruitment of the first 12 patients is complete, the DMC will review the safety data and inform whether the staggered recruitment should continue.** **All DMC reports will be duly notified to the ANMAT.**
Pharmacokinetic assessments	**A PK sub-study will be carried out on 20 subjects. A blood sample will be drawn for Pharmacokinetic tests immediately before the 1st. administration of the study drug, at the end of the 1st. administration of the study drug, immediately before the 2nd administration of the study drug, at the end of the 2nd study drug administration, 24h after 2nd study drug administration and 7 days after 1st. study drug administration.**
Discontinuation criteria	**The study medication will not be discontinued due to progression of disease.** **Discontinuation from the study drug must be done in case of an allergic reaction > = grade 3 and/or anaphylaxis**

Standard of care/ medication	**Standard of care:** • **Hospital** • **Guidelines from the Ministry of Health of Argentina:** **Treatment:** **There is no specific treatment recommended for COVID-19 infection. Patients infected with COVID-19 must receive care to alleviate symptoms. For severe cases, treatment must include support of vital functions. In accordance with the recommendation of the Ministry of Health, the use of treatment that does not have scientific evidence should be used in the context of research studies.** **Prohibited medication: medication that is being administered in the context of a clinical trial.** **All treatment with a therapeutic objective against SARS-CoV-2 must be reported to the medical monitor.**
Statistical procedures	**Sample size** **Assuming a 70% "standard of care" event rate (Wang 2020, https://doi.org/10.1016/S0140-6736(20)31023-0) and an absolute effect size of 15 percentage points, for a power of 80% and an error α = 0.025 (for a one-tailed comparison), 121 subjects will be required in each treatment group, totalling 242 participating subjects.** **Interim analysis** **An interim analysis will be carried out after 60% of recruitment has been reached; that is, approximately after the end of the follow-up of the first 145 subjects. The Data Monitoring Committee will analyse the event rate in the group under the "standard of care" and may recommend: (1) modifying the sample size, based on the observed event rate, or (2) stopping the study if: (2.a) it's considered that it is not feasible because it requires an excessively large sample size or (2.b) it's considered futile because of an event rate ≥ 95%.** **The re-estimation of the sample size will allow the sample to be increased by up to 72 subjects, to reach 314 subjects. The requirement of a greater number of subjects would be considered "Not Feasible" and will cause the study to be stopped.** **Analysis set** **The Full Analysis Set (FAS) will be made up by all the subjects randomised to INM005.**

The modified intent-to-treat group will be made up of all subjects who have been randomised to receive INM005 and who have received the full treatment regime of INM005. This will be the primary population for all efficacy analysis.

The Per Protocol population will be made up by all the subjects in the mITT who have no major protocol deviations. Major protocol deviations will be reviewed and subjected to determination prior to closing the database and breaking the blind. The PP population will be used for the endorsement sensitivity analysis.

The Safety Population will be made up of all subjects who have received at least 1 dose of INM005. This population will be used for all summaries of accounting data, baseline and demographic characteristics of subjects, and safety information, including incidence of adverse events.

Statistical analysis

Differences between patients in both treatment groups in the proportions of the primary and secondary efficacy endpoints will be analysed using the Chi-square test. The differences between these groups in the endpoints that involve the time to the occurrence of the events will be analysed using the non-parametric Mann-Whitney test. Antibody levels will be compared using a Levine’s fit T test, if necessary. The main analyses will be carried out in the mITT population and the sensitivity analyses in the PP population.

For the exploratory analysis of the change in laboratory variables predictors of disease progression, a multivariate logistic regression analysis will be used.

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LIST OF FIGURES

ABBREVIATIONS

Abbreviation	Definition
ACE	angiotensin converting enzyme II
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AF/CF	Assent form/ consent form
ALT	alanine aminotransferase
ANMAT	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (National Administration of Drugs, Food and Medical Technology)
ARDS	Acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC0-inf	area under the curve of concentration over time extrapolated to infinity
BMI	body mass index
Btk	Bruton tyrosine kinase
C	Centigrade
cGAS	MP-AMP synthetase
Cmax	maximum concentration observed
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system

COVID-19	Coronavirus disease
CreatS	serum creatinine
CRF	Case Report Form
CRP	polymerase chain reaction
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data monitoring committee
EC	Ethics committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	End of study
ESR	erythrocyte sedimentation rate
ET	Early termination
EU	European Union
FDA	Food and Drug Administration

FiO2	Fraction of inspired oxygen
g	grams
GCP	Good Clinical Practices
h	hour(s)
Hb	haemoglobin
Hct	haematocrit
HGF	hepatocyte growth factor
HIV	Human immunodeficiency virus
i.v.	Intravenous
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use
ICU	Intensive care unit
IFN-a/b	type I interferons
IL	Interleukin
IMP	Investigational medicinal product
IRB	Institutional Review Board
IRF3	interferon regulator factor
Jak1	Janus kinase 1

kg	kilogram
l	litres
LDH	lactate dehydrogenase
MCSF	monocyte colony stimulating factor
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East respiratory syndrome-related coronavirus
mg	milligram
min	minute
mITT	modified intent-to-treat
MRA	Mechanical ventilation
Na	sodium
NCA	non-compartmental analysis
NF-KB	nuclear transcription factors KB
NIH	National Institute of Health
NIPPV	non-invasive positive pressure ventilation
PaCO2	partial pressure of carbon dioxide
PaO2	partial pressure of oxygen
PK	pharmacokinetics
PP	Per Protocol

PT	preferred term
RBC	red blood cells
RBD	Receptor binding dominion
RIG-I	retinoic acid inducible gene-like RNA receptor
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SatO2	Oxygen saturation
SBP	supine blood pressure
SoC	Standard of care
SOFA	Sequential organ failure assessment
TEAE	treatment emergent adverse event
TLR	Toll-like receptors
t_{max}	time until maximum concentration
Tyk2	tyrosine kinase 2
ULN	upper limit of normal
US	United States
V	visit

Vd	volume of distribution
w	week(s)
WBC	white blood cells
WHO	World Health Organisation

1 INTRODUCTION AND RATIONALE

1.1 Context

1.1.1 DISEASE

Etiology and epidemiology

The pandemic caused by the novel coronavirus has generated an unprecedented situation in recent history, with several million infected and hundreds of thousands of deaths. Although there have been reports of respiratory infections due to COVID-19 as from December 2019, the WHO declared the infection caused by coronavirus called COVID-19 a pandemic in March of this year (1-3).

Coronavirus disease (COVID-19) is caused by SARS-CoV-2, a zoonotic, positive-sense, single-stranded RNA betacoronavirus that has a protein envelope structurally related to SARS-CoV (the coronavirus that causes a severe and acute respiratory syndrome) and MERS-CoV (Middle East respiratory syndrome-related coronavirus) (4). SARS-CoV-2 and SARS-CoV bind to the angiotensin-converting enzyme II (ACE2) receptor to enter lung and intestinal epithelial cells; after binding to the receptor, they fuse with the cell membrane and release viral RNA (5-7).

Once released, the RNA is recognised by Toll-like receptors (TLR); it forms complexes with the retinoic acid-inducible gene-like RNA receptor (RIG-I), the cytolosic receptor for melanoma differentiation-associated protein 5 (MDA5) and cyclic GMP-AMP nucleotidyltransferase synthetase (cGAS) in the cytoplasm and stimulate signalling cascades that activate nuclear transcription factors like factor-κB (NF-κB) and interferon regulatory factor (IRF3) with the production of type I interferons (IFN-a/b) and pro-inflammatory cytokines (8, 9). Both infected pneumocytes and macrophages produce IL-6, IL-8, MCP-1, TGF-β1 and other cytokines and inflammatory mediators responsible for the immune response and the limitation of infection; however, this pathway may also be responsible for the pulmonary damage in the context of the cytokine storm (8-11).

The production and release of pulmonary and systemic cytokines, stimulated in part by the IL-6 pathway or the JAK/STAT signalling pathway, is related to the infiltration of activated neutrophils into the alveolar space, followed by a phase with interstitial fibrosis that can take a long time to resolve. In severe cases, this time can be important not only due to the availability of resources but also due to the complications that individuals requiring ICU hospitalisation and mechanical ventilation may have (10-15).

The virus has a highly contagious capacity and can be transmitted by human-human contact with reproduction rates of around 2.2, meaning that its growth can be exponential in the community. The basic reproduction number (R 0) defined as the average number of secondary cases that a primary case can generate in the susceptible population according ranges from 1.4 and 2.5; although its value varies in reports due in part to the different methods used, geographic areas, and sample sizes, it suggests that SARS-CoV-2 has a high propagation capacity (16-20). The control strategies implemented related to avoid close contacts between people have had different degrees of compliance and in some countries, they have managed to avoid the peak of cases, and the collapse of the health system. Over 8,900,000 cases and 466,500 deaths have been reported worldwide (22.06.2020) and the numbers continue to grow (21). This scenario has raised challenges not only in the Health system but also at governmental level since the measures taken will impact not only on Health but also on socioeconomic aspects.

1.1.1.1 Clinical Presentation

The incubation period varies between 3 and 7 days, although periods of more than 14 days have been observed; while the average time between the onset of symptoms and the diagnosis is 4 to 6 days and may coincide with the time to the first consultation (2-9 days). The main transmission route is from person to person and occurs in a similar way to influenza. An infected person who coughs, sneezes or speaks, eliminates viral particles that travel inside respiratory secretion droplets (in general for no more than 2 meters) which then come into direct contact with the mucosa of another individual, transmitting the disease; it can also occur if a person touches an infected surface and then the eyes, nose, or mouth (22).

The most common symptoms are fever, cough, dyspnoea, headache, odynophagia; gastrointestinal disorders such as diarrhoea, nausea, vomiting or asthenia, dysgeusia and anosmia have also been described (23-25).

Pneumonia is the most common severe manifestation of the infection, characterised by fever, cough, dyspnoea, and bilateral infiltrates on chest imaging; in the most severe cases, they can mainly evolve in the second week from the onset of symptoms to respiratory failure with different degrees of severity, including the need for mechanical ventilation in the intensive care unit (ICU) (22-25).

Severe conditions can also affect the liver, kidney, heart, oesophagus, bladder, ileum, pancreas and progress to septicaemia, coagulopathy, septic shock and multi-organ failure with a high mortality rate depending on age and comorbidities amongst other factors. The acute respiratory and other organs damage is associated with the "cytokine storm" as seen in patients with SARS-CoV and MERS-CoV pneumonia, in which levels of IL-6 and other pro-

inflammatory cytokines correlate with the clinical and radiographic severity picture of the clinical picture (26, 27).

In most patients, COVID-19 presents itself with either mild or asymptomatic condition; it is estimated that 15.7% of patients undergo a severe form of the disease and mortality in critical cases that progress with the need for ICU is 37-50% according to different series (26, 27). The cytokine storm triggered in COVID-19 and the patient´s clinical condition could be responsible for the damage to the lung and other organs. In patients with severe pneumonia, conditions include lymphopenia, elevated CRP with normal levels of procalcitonin, elevated LDH with decreased albumin, as well as elevated levels of IL-6 and other mediators such as IL-1, IL-2, IL-4, IL-7, IL-10, IL-12, IL-13, IL-17, GCSF, monocyte colony stimulating factor (MCSF), IP-10, MCP-1, MIP-1α, hepatocyte growth factor (HGF), IFN-γ and TNF-α (28-31).

The laboratory findings that have been frequently detected in patients diagnosed with COVID-19 (especially in severe forms) are hypoalbumin (75%), increased C-reactive protein (58.3%), increased lactate dehydrogenase (LDH, 57%) , lymphopenia (43.1%), and increased globular sedimentation rate (GSR, 41.8%) (26).

The majority of patients with pneumonia present bilateral infiltrates (72.9%) with ground glass opacities, particularly on chest computed axial tomography (CT). The distribution of infiltrates with areas of consolidation can be located in the sub-pleural as well as the pulmonary lobe areas and then progress to diffuse bilateral opacities in severe cases (32).

Determination of RT-PCR in nasopharyngeal/oropharyngeal swabs, sputum and other respiratory secretions, blood and faeces is one of the main techniques to detect the SARS-CoV-2. Despite its good sensitivity and specificity, false negative reactions may occur, which is why it is sometimes necessary to take samples on more than one occasion. Techniques are currently being developed with the aim of solving this problem, reducing costs, and reducing times to obtain the test results (33).

1.1.1.2 Risk factors

Older people with high blood pressure, asthma, diabetes, and other underlying diseases have a significantly higher risk of infection. A 36.8% of patients with SARS-CoV-2 infection have underlying non-communicable diseases, the most frequent of which are high blood pressure (18.6%), cardiovascular diseases (14.4%) and diabetes (11.9%) (26). It has also been observed that people with blood group A have a higher risk of infection as compared to those with blood group non-A, while blood group O has a significantly lower susceptibility to infection as compared to non-O blood groups.

Older age (particularly over 60 years) and underlying diseases (diabetes, high blood pressure, heart disease, obesity, chronic lung disease, cerebrovascular disease, chronic kidney disease, immunosuppression, and cancer) increase the likelihood of severe illness and death. In a meta-analysis that included 77,932 patients, male sex was associated with morbidity (OR = 1.12; 95% CI: 1.01–1.25), severity (OR = 1.63; 95% CI: 1.28–2.06) and mortality (OR = 1.71; 95% CI: 1.51–1.93) (26, 34).

Recently, information has been published that relates the presence of the HLA-B*46:01 allele to a greater severity of the clinical picture, probably linked to the lower capacity to present the SARS-CoV-2 epitopes (35).

1.1.1.3 Stratification by risk

The clinical classification (NIH) according to the severity level of the COVID-19 condition is divided into (36):

1. **Mild cases**

   -Clinical symptoms are mild and imaging show no sign of pneumonia.

2. **Moderate cases**

   -Patients who have evidence of lower respiratory disease by clinical evaluation or imaging and an oxygen saturation (SpO2) ≥ 94% in ambient air.

3. **Severe cases**

   - Patients who meet any of the following criteria:

     -Respiratory failure (≧ 30 breaths/min)

     -Oxygen saturation ≤ 93% at rest

     -Partial pressure of arterial oxygen (PaO2)/fraction of inspired oxygen (FiO2) ≦ 300 mmHg (l mmHg = 0.133kPa)

     -Images of the chest that show progression > 50% in 24-48 hours

3. **Critical cases**

   Patients who meet any of the following criteria:

-Respiratory failure with need for mechanical assisted respiration

- Shock

-Other organ failure that requires care at the ICU

1.1.1.4 Situation in Argentina

According to the Ministry of Health, in Argentina 23 provinces are affected, more than 59,000 cases were diagnosed, most in CABA (i.e. the Buenos Aires metropolitan area) and the province of Buenos Aires; and more than 1,000 deaths, of which the majority are over 60 years old. The array of measures adopted at government level has managed to avoid the excessive growth in the number cases and has allowed the health system to respond to the growing demand. Despite these measures, both in the public and private sub-sectors, the number of admissions to ICU beds is still high, increasing diagnoses and consultations, so the measures adopted are susceptible to change according to the evolution of the situation (37).

1.1.2 Treatment approaches

No effective therapies for the treatment or prevention of SARS-CoV2 have been identified yet. Preliminary evidence indicates that passive immunotherapy with convalescent plasma could alter the clinical course of this infection in a favourable manner. This strategy, even if confirmed as successful, requires voluntary donation by patients who have recovered, not all of whom are eligible as donors, since the antibody response varies in magnitude in different patients (38-44).

1.1.2.1 Symptomatic therapy

Clinical management of hospitalised COVID-19 patients includes supportive treatment: supplemental oxygen therapy, antipyretics, empirical antimicrobials, neuraminidase inhibitors for the treatment of influenza when there is local circulation, and intensive care as needed. In patients with a mild condition, isolation, antipyretics and evolutionary control are mainly indicated, while in those patients who must be hospitalised, the use of additional measures such as those previously mentioned is considered.

1.1.2.2 Specific treatments

Currently there is no specific antiviral treatment and no vaccine available; all molecules are under evaluation, some of them in more advanced stages. Therapeutic targets include virus binding, inhibition of specific enzymes involved in replication, transcription, helicases and

proteases, siRNA, antisense RNA and ribozyme or neutralising antibodies or even monoclonal antibodies directed at the host receptor or interfering with S1, amongst others (38).

Remdesivir demonstrated in the preliminary results of a double-blind, randomised, placebo-controlled trial (n = 1063) greater efficacy in mean recovery time, 11 days (95% CI: 9-12), compared to 15 days (CI 95%: 13-19) of those who received placebo (recovery rate index, 1.32; 95% CI, 1.12-1.55; p <0.001). On the other hand, in mortality at 14 days, the difference between the two arms was smaller, 7.1% with remdesivir and 11.9% with placebo (HR: 0.70; 95% CI, 0.47 to 1.04). The results of studies in which remdisivir is used as part of a combination therapy are currently awaited (39).

Lopinavir/ritonavir is a protease inhibitor drug approved for the treatment of HIV infection; in a 2-arm, randomised, controlled, open-label study it was compared with standard management for patients hospitalised for severe Covid-19 disease (n = 199). In the study, no differences were observed in the time for clinical improvement (1.31; 95% CI: 0.95-1.80, p = 0.09), nor were differences in mortality at day 28 (19.2% vs. 25.0%; risk difference: −5.8; 95% CI: −17.3 to 5.7). However, when considering the sub-group of patients who started treatment early in a post-Hoc analysis the lopinavir/ritonavir group tended to be better than standard treatment although it was not statistically significant in the end. As the sample size was not calculated taking into account the multiplicity of hypotheses, the authors speculate that the study did not have enough power to demonstrate differences in this sub-group. The results of other studies such as Solidaridad that incorporated lopinavir ritonavir into one of its branches are currently awaited (40).

The combination of lopinavir/ritonavir and interferon-1β is being evaluated as it demonstrated anti-MERS-CoV activity in vitro and in an in vivo study carried out in common marmosets they had better results than untreated animals. Favourable responses have also been found with the combination lopinavir/ritonavir-ribavirin, we will probably have more information on these combinations in a short time (38).

Interferon alpha-1 activates the phosphorylation of Janus kinase 1 (Jak1) and tyrosine kinase 2 (Tyk2) initiating the expression of immunomodulators and the expression of antiviral proteins; some publications have shown antiviral activity of IFN-α and IFN- β and IFN-α / β, IFN-β 1a and IFN-γ combinations against SARS-CoV. These combinations could also be effective against SARS-CoV-2 and are under assessment (38).

Oseltamivir is a neuraminidase inhibitor that has been used as an empirical drug for COVID-19, although there is no evidence of its efficacy in clinical trials yet; it is also included within the therapeutic strategy for the treatment of influenza (38).

Chloroquine is an antimalarial drug that can inhibit both virus-host cell interaction and pH-dependent virus replication. Studies have been published that include branches of treatment with chloroquine and hydroxychloroquine with or without azithromycin, but which have the difficulty of having included the same few individuals; additionally, in a meta-analysis it was observed that the individuals who received these drugs had a higher risk of serious adverse events, particularly cardiological, although this information is under review (41).

The use of convalescent plasma is a passive immunotherapy method, which was used for SARS in 2003 and for MERS in 2012, and has been proposed as a treatment for COVID-19. In the case of SARS-CoV in 2003, the antibodies of individuals who were cured could persist in high concentrations for long periods of time and could be a treatment option in SARS-CoV-2 2020 (42-44).

There is evidence in a small number of patients that this strategy could be effective in individuals with pneumonia or severe conditions. However, this depends on maintaining a sufficiently high antibody titre in donors and on developing production and supply strategies, as well as validating these findings with clinical trials with the appropriate design on a larger scale (38, 42-44).

Although SARS-CoV-2 is an emerging pathogen, it has high homology with SARS-CoV and MERS-CoV, so research and development of novel coronavirus vaccines can be based on the methods used in SARS and MERS. Studies have begun for mRNA vaccines, recombinant proteins, viral vectors, DNA, among others, and some of them have continued to testing phase in humans; however, it remains to be determined whether the production of specific antibodies is related to the rapid elimination of SARS-CoV-2 and what is its impact on the community in terms of blocking the infection and the immune response of the individual (44).

Monoclonal antibodies have shown activity against SARS, for example, the CR3022 molecule binds effectively to the receptor-binding domain (RBD) of SARS-CoV-2 and prevents interaction with receptor proteins of human cells such as ACE2. Other fusion proteins with high affinity to the extracellular domain of human ACE2 with activity against SARS-CoV and SARS-CoV-2 are being evaluated. This therapeutic target is under development. It will be very important to consider the adverse events of this group related to the immune response (38, 44).

Different molecules that act trying to avoid the damage caused by the release of cytokines, such as IL 6 inhibitors (tocilizumab, sarilimumab amongst others), IL2 inhibitors, JACK inhibitors (e.g. Ruxolitinib) or Bruton's tyrosine kinase (Btk) inhibitors such as acalabrutinib are under evaluation (38, 44).

The preliminary results of the Recovery study, a randomised, controlled, open-label, adaptive platform clinical study with 5 arms, demonstrated the benefit of the dexamethasone 6 mg oral or intravenous arm for 10 days (n=2104) compared with those receiving standard treatment (n=4321). The study observed lower mortality (RR 0.76; 95% CI: 0.6-0.96; p=0.021) in those patients with pneumonia who required oxygen (RR 0.8; 95% CI: 0.7-0.92; p <0.002) or were on mechanical ventilation (RR 0.65; 95% CI: 0.51-0.82; p <0.001) who received dexamethasone (45).

1.1.2.3 Support treatment

In patients with COVID-19 pneumonia, dyspnoea is variable and does not always correlate with oxygen levels in the blood, so oxygen therapy must be guided by other parameters. A recent randomised trial compared patients receiving oxygen therapy; a branch whose oxygen saturation objective was ≥ 96% and another conservative branch whose saturation objective was 88-92% had to be stopped prematurely due to the poor benefit of the conservative branch. In patients with oxygen requirements, the indication for nasal cannulas and masks with different inspired oxygen fractions is defined based on the oxygen levels in the blood measured through oxygen saturation or blood gases. There is evidence that the high flow of oxygen and the change to prone position of the patient while receiving oxygen therapy are alternatives in these strategies that could be useful and are being evaluated (46, 47).

Non-invasive positive pressure ventilation (NIPPV) is an option that does not require endotracheal intubation in patients who can remain awake. Although this strategy has the advantage of not being invasive, in a retrospective case series from Wuhan, 72% of patients with NIPPV died. The benefit of this technique is unclear so its usefulness is limited, in addition to the risk associated with aerosolisation, which is difficult to quantify (46, 48).

Whether to start mechanical ventilation early or later is debated, some prefer to wait based on the mortality rate of intubated patients, while others argue that early ventilation would prevent further lung damage. It is recommended that the mechanical ventilation modality be the same as for patients with acute respiratory distress syndrome (ARDS) of other causes; fundamentally with low pressures in the airway and low lung volumes (46).

1.1.3 Investigational medicinal product

INM005 is an animal-source haemoderivate. The active ingredient is the F(ab')2 purified from total equine immunoglobulins. These immunoglobulins were obtained from a pool of sera from horses previously immunised with the glycoprotein S (Spike Protein) RBD (Receptor Binding Domain) of SARS-CoV-2 , as illustrated in Figure 1, obtained by genetic

engineering techniques. The RBD is obtained in the laboratory through biotechnology techniques and is responsible for the binding of the virus to the Angiotensin-converting enzyme 2 (ACE2) receptor through which the virus is internalised in the cell (49-50).

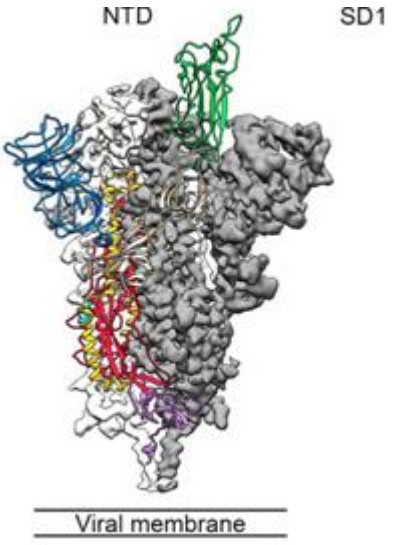
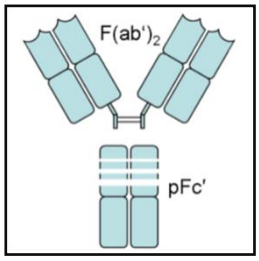


Figure 1. Tridimensional model of the Spike protein, in green is the receptor-binding domain (RBD) of the Spike glycoprotein

Adapted from Wrapp D. et al, 2020 (65).

The F(ab')2 fragments are obtained from the digestion of the total equine immunoglobulin fraction with the enzyme pepsin. The process includes a subsequent removal of the immunoglobulin constant region, keeping the hinge region intact (Figure 2). F(ab')2 fragments have two F(ab) binding domains connected by a disulphide bridge and are therefore divalent, with a molecular weight of approximately 110 kiloDaltons.

Figure 1.2 Schematic representation of an immunoglobulin with the F(ab')2 fragments linked by disulphide bridge



In vitro assays using Vero E6 cells have shown that INM005 has a very high titre of neutralising anti-SARS-CoV-2 INM005 F(ab’)2 antibodies (1:10240) (51). The proposed mechanism of action for the investigational medicinal product (IMP) is the blockade of the virus entry by means of binding the IMP to the viral S protein RBD, in this way the virus cannot be internalised and the cytopathic effect is avoided.

The IMP would be administered within the first days after the onset of symptoms and after the diagnosis of the disease is confirmed. The efficacy of an equine serum in humans lies in its capacity to neutralise the virus in the bloodstream of infected individuals.

The use of this type of antibody would constitute a fast and effective therapeutic strategy since it has the advantage of recognising a wide variety of epitopes on the antigen - thus limiting the risk of mutations that lead to a possible viral evasion. Besides, they tend to develop higher avidity relative to monoclonal antibodies for a given antigen. Although the use of equine sera has been associated with disease risk in the past, the new generation of F(ab')2 fragments have been shown to be safe and well tolerated in humans. The F(ab´)2 are easy to produce, allowing the scaling up for rapid product availability (55, 65).

In this context, at present, the use of convalescent plasma is the only possible immunotherapy for hospitalised patients with COVID-19 (66-68). However, there are some limitations on the availability of these plasmas. On the one hand, specific antibodies against the virus with neutralising potential generally appear 2 to 3 weeks after the onset of symptoms in patients. On the other hand, its extraction depends on the donation of plasma from patients already recovered without viral load. Furthermore, various studies show great variability in the response of neutralising titres between individuals and even the efficacy in critical patients in the ICU has not been fully demonstrated (66, 70). In contrast, the use of F(ab')2 fragments

developed using RBD as antigen, rather than the whole Spike protein or the whole virus, avoids the injection of other antibodies against other Spike domains that can lead to unwanted adverse events, such as enhancing the infection through what is known as antibody dependent enhancement (ADE) (71). The results of the *in vitro* seroneutralisation tests have shown that INM005 is around 50 times more potent than the average observed with convalescent plasmas, which allows the use of a smaller amount of product with neutralising capacity (51).

INM005 is very similar to other antitoxins such as those used for diphtheria and tetanus, which have been successfully used since 1890. Recently, the United States Food and Drug Administration (FDA) has approved a product based on an equine hyperimmune antibody fragment that specifically neutralises toxins produced by *Clostridium botulinum*; the trade name of this product is BAT®, and its approved indication is the treatment of symptomatic botulism (72). We believe that a therapeutic approach similar to this one can be used to prevent the progression of COVID-19 disease.

1.1.4 Rationale for the use of placebo

The development process for the proposed protocol included consideration of the need for a placebo group combined with standards of care as a concurrent control in a fully blinded study. It should be noted that the body of literature related to this indication, as well as the serious nature of this disease, provide a potential clinical justification for choosing a study design that includes a placebo control, under the presumption that there are no other available means of active drug therapy.

In the first place, the inclusion of a placebo group in this indication, combined with the standard of care (SoC), is not considered a decision contrary to the interests of the patient from the clinical perspective, since there is currently no preventive or acute treatment for the treatment of COVID-19. All subjects randomised to the treatment groups within this study will receive the best options from the current standard of care of the institution where they are hospitalised.

Finally, there is no active treatment (of proven efficacy) to estimate placebo event rates consistently. Furthermore, the experimental intervention (INM005) for this study does not have previous data on efficacy or safety in a population with COVID-19.

As a result, a concurrent placebo control group combined with the best standard of care options will be included in the proposed study, and a clinical break-even point is maintained between the treatment groups.

1.2 Study rationale

Treatment of COVID-19 is basically symptomatic. There is no specific treatment capable of preventing or controlling the damage caused by SARS-CoV-2.

The pandemic caused by the novel coronavirus has generated an unprecedented situation in recent history, with several million infected and hundreds of thousands of deaths. This disease is easily transmissible by air. Although a high percentage of patients have a mild clinical presentation, approximately 15% of them present moderate to severe cases and 5% require intensive care with mechanical ventilation and face a high risk of mortality. No effective therapies for the treatment or prevention of SARS-CoV-2 have been identified so far. Preliminary evidence indicates that passive immunotherapy with convalescent plasma could favourably alter the clinical course of this infection. This strategy, even if confirmed as successful, requires voluntary donation by patients who have recovered, not all of whom are eligible as donors, since the antibody response magnitude varies amongst different patients.

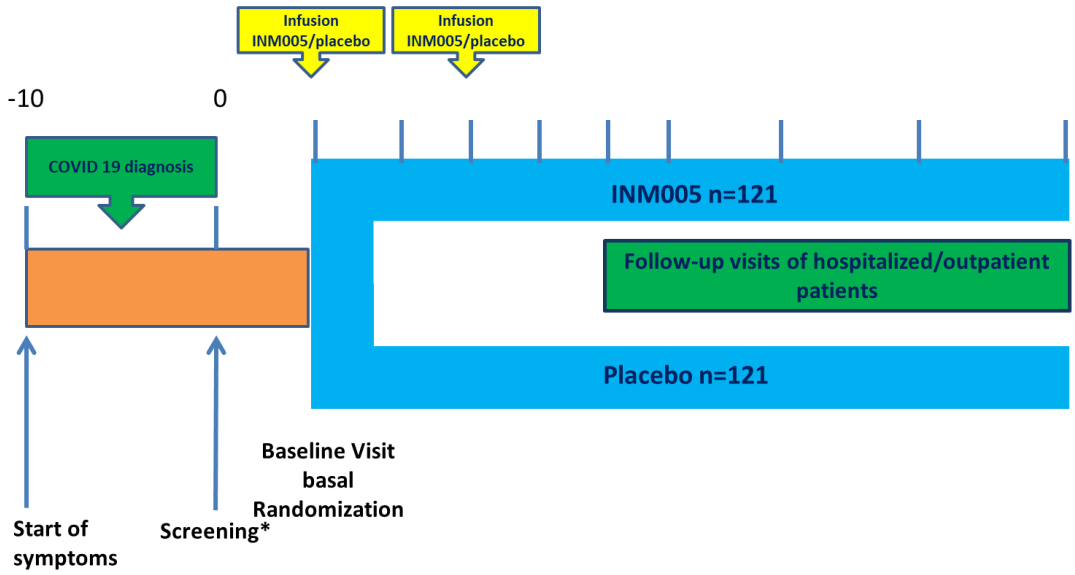
This study aims at studying the efficacy and safety of passive immunotherapy by administering hyperimmune serum INM005 generated by the antigenic stimulation of equines. INM005 is a product that is biologically equivalent to the anti-Shiga toxin serum INM004 that neutralises the interaction of SARS-CoV-2 with its cellular receptor, thus preventing virus multiplication. The safety information for the anti-Shiga toxin serum INM004 indicates that it is well tolerated and that no serious adverse events or suspensions of treatment have been detected.

INM005 is being developed for the treatment of COVID-19 infection. It is anticipated that INM005 treatment should be initiated for a SARS-CoV-2 infection diagnosed on the basis of laboratory results early in the onset of the disease. This is likely to be the recommended paradigm after conducting clinical studies, as these patients are most likely to benefit from the use of neutralising anti-SARS-CoV-2 antibody fragments. Therefore, this product could be used in patients with a clinical manifestation of moderate to severe disease of COVID-19. An early interruption of the cascade mediated by virus entry into cells is expected to prevent the development of disease progression and reduce the severity of the condition, the rate of complications, and the incidence/duration of hospitalisations. Therefore, the proposed research will evaluate patients who are in the early stages of this disease, that is, patients who attend a medical consultation as a result of a SARS-Cov-2 infection prior to the development of a highly advanced condition of the illness.

INMUNOVA hypothesised that patients between 18-79 years of age with SARS-CoV-2 infection would be the ones most likely to benefit from INM005 treatment administered to improve the symptoms of COVID-19. The proposed INM005 administration regimen is only

after PCR confirmation of the presence of SARS-CoV-2 in the patient's clinical sample (Figure 1.3).

Figure 1.3 Administration regime proposed for INM005*



*Reference: From the start of the symptoms until the screening visits there is a 10-day maximum window; from the screening visit t the baseline visits there is a 24-hour maximum window.

The objective of this adaptive Stage II/III study is to demonstrate the efficacy and safety of INM005 in terms of improving the clinical course of COVID-19, at 28 days after the start of treatment with the investigational product in individuals with moderate to severe disease requiring hospitalisation.

1.3 Preclinical safety and clinical support data

Observations supporting the exposure of an adult population to INM005 within the framework of the proposed investigation include preclinical and clinical evaluations of INM004 and related compounds.

1.3.1 F(ab')2 fraction of equine immunoglobulins

Passive immunotherapy is one of the most promising therapeutic strategies to reduce the lethality and morbidity of the pandemic. Anti-venoms and antitoxins in the form of equine

F(ab')2 fragments have been used for more than 30 years. Therefore, the safety profile of products of similar structure but with different specificity is well known in adults and children, and is generally considered manageable, as they have been used without the occurence of significant adverse events.

The product INM005 is made with the same technological platform with which the Shiga antitoxin has been made, and fractions of F(ab’)2 of viper venom neutralising equine immunoglobulins have been made for more than 30 years. The difference for each product lies in the initial antigen (venom/toxin) with which the horses are immunised, and therefore in the main specificity of the antiserum.

The products having different specificity cannot be structurally distinguished by performing complex physicochemical analytical techniques (electrophoresis, chromatography) and a challenge against the antigen used in immunisation is required for their recognition.

For the reasons explained, this type of biological product differs widely from synthetic chemical products and from biological products obtained by recombinant DNA technology (biotechnological) in which homogeneous protein preparations are mostly obtained with a low percentage of variations at the level of molecular modifications.

Particularly in Argentina, the Instituto Biológico Argentino S.A.I.C. - BIOL (manufacturer of the investigational product), has produced this type of preparations derived from equine plasma since 1908 and since 1984 it has used the same procedure to elaborate the fraction F(ab´)2 purified from horse plasma that is injected to over 1000 patients every year for the treatment of snake poisoning.

It is important to note that the product is not innovative in its structure, but rather in its specificity of recognition towards SARS-CoV-2. As for the anti-Shiga toxin product (INM004), the anti-SARS-CoV-2 serum will be formulated at a lower concentration of the equine active ingredient F(ab´)2 than the current BIOL formula for antivenin (2.5% versus 6%) and consequently there will be a lower degree of exposure to the product and its possible adverse reactions.

Although the product is not strictly an anti-venom, it is produced as such and it is proposed to be used in a similar way, that is, to neutralise the interaction of SARS-CoV-2 with its cellular receptor, preventing the multiplication of the virus and therefore, the COVID-19 disease. This is why, both for the production and for the control and regulation for INM005, we rely on the World Health Organisation guide for the production, control and regulation of anti-venom immunoglobulins. The current version is the 2016 edition (52). Chapter 18, devoted to the clinical evaluation of anti-venoms, begins by explaining how unusual anti-venoms are compared to other pharmaceutical agents. Then, it explains the standard pathway

for the clinical evaluation of new therapeutic products and suggests that the relevance of this pathway for anti-venoms depends on a number of factors, mainly, whether an anti-venom is new or has previously been used in human patients, the ethical basis for the study, the feasibility of conducting such studies, as well as ethical and national regulatory considerations. Section 18.1.2 Phase I studies states “Conventional clinical studies using healthy volunteers are not appropriate in the case of anti-venoms due to the risk of anaphylactic and other reactions (e.g. pyrogenic or serum diseases, and rarely hypersensitivity reactions to equine/sheep plasma proteins) and the risk of generating sensitisation to equine/sheep plasma proteins in healthy volunteers”. Phase I studies, designed mainly to detect unanticipated adverse reactions, would not apply in this case due to previous experience with INM004 (manufactured with the same technological platform) and other anti-venoms and antitoxins.

Therefore, in the case of INM005, as it is the biologically equivalent product to anti-Shiga toxin serum, it would be coherent to follow these guidelines for its regulatory development. Also using the results obtained in the clinical development for the latter. During this development program, INMUNOVA has carried out several preclinical tests, in accordance with the guidelines established by ICH S6, which included 10 toxicology studies with more than 500 animals. A standard tissue cross-reactivity (TCR) test was performed with 34 frozen tissues. In the case of Shiga toxin, no safety concerns were reported in any of these preclinical studies. Then in 2017, a first trial in humans was conducted with 14 healthy adult volunteers (clincaltrias.gov identifier: NCT03388216) that showed an excellent safety profile, in which there was no hypersensitivity event reported in the 30-day safety follow-up period for the subjects of the single and repeat dose stages. Additionally, in the samples of the evaluated subjects there is no evidence of a change in the reactivity towards the product (reactivity against Equine Ig) in serum samples taken 30 days after the administration of both single and repeated doses.

Taking into account these antecedents with INM004, and added to the results of the study with convalescent plasma in 5000 patients in the US, where it was demonstrated that the incidence of serious adverse events after infusion was less than 1% (7), it is assumed that there is no cross-reactivity of anti RBD (human convalescent plasma) antibodies and human tissues.

Since October 2019, INMUNOVA has been conducting a phase II/III clinical trial to evaluate the safety and efficacy of INM004 in paediatric patients with Shiga toxin-positive bloody diarrhoea for the prevention of haemolytic uremic syndrome (clincaltrias.gov identifier: NCT041323 75). Recruitment to date has been 11 children and no safety findings have been reported (currently the enrolment of this trial is suspended due to the pandemic, see section 1.3.5- semi-annual safety report).

1.3.2 F(ab’)2 fraction of equine immunoglobulins - similar products

As mentioned above, antivenins and antitoxins in the form of equine F(ab')2 fragments have been used for more than 30 years as anti-tetanus and antivenin sera. The safety profile of similar products is well characterised. Currently, the products listed in Table 1.1, which are similar to INM005, are approved by the FDA and also in the European Union (EU):

Table 1.1 Products similar to INM005 approved by the Food and Drug Administration (FDA) and European Union

Product	Company	Application	Type	Approval by the EU/FDA
FAVIRAB®	Sanofi Pasteur S.A.	Post-exposure prophylaxis to Favirab in subjects with suspected exposure to the Favirab virus, particularly in the case of severe exposure	F(ab')2 of equine immunoglobulin (antirabies)	EU
Anascorp®	RDTX Inc.	Centruroides (scorpion) sting	F(ab')2 of equine immunoglobulin	FDA 2011
BAT®	Emergent Biosolutions	Heptavalent botulinus antitoxin (A, B, C, d, E, F, G)	F(ab')2 of equine immunoglobulin	FDA 2013
Anavip™	RDTX Inc.	Crotalid bite	F(ab')2 of equine immunoglobulin	FDA 2015

1.3.3 F(ab’)2 fraction of equine immunoglobulins - Safety information of similar products

Purification methods were introduced in order to reduce the frequency of reactions to antivenin, through the elimination of the Fc fragment of IgG, which prevents complement activation and could perhaps reduce the intensity of complex formation responsible for the appearance of late reactions to antivenin (serum sickness). The F(ab')2 fragments of immunoglobulins have been widely used for 60-70 years. However, it was the aggregation of antivenin proteins, and not the activation of complement mediated by the FC fragment, that was increasingly identified as the main cause of antivenin reactions. Therefore, regarding the safety of antivenins, a critical issue is probably the physicochemical characteristics of the

antivenins and not exclusively the type of neutralising molecules that constitute the active ingredient. It is also important to ensure that currently available methodologies for antivenin production provide a sufficient margin of safety with regard to the potential risk of zoonosis transmission (53).

In 2013, a series of clinical studies carried out in a significant population of patients was published as part of the development of Anascorp (an antivenin indicated for the treatment of scorpion sting poisoning). These consisted of five prospective clinical studies and one historical-controlled case study that together included a total of 1,534 patients with a wide range of ages (from less than 1 month of age to 90 years of age) (54). The patient population included 802 men and 732 women; 307 people > 18 years of age and 1,118 patients between 0 and 18 years of age.

Monitoring of vital signs and adverse reactions, including acute hypersensitivity reactions and serum sickness, was performed in all patients. Follow-up telephone interviews were conducted at 24 hours, and 7 and 14 days after the administration of the treatment to obtain data on symptoms that could suggest the existence of a poison effect, the presence of serum sickness, or any other adverse reaction. In the patients studied, the most commonly observed AEs were vomiting, pyrexia, rash, nausea, and pruritus. The incidence of these AEs was greater than 2% but less than 5%.

Table 1.3 shows the AEs that occurred in patients in all clinical studies conducted on Anascorp. 27% (421/1534) of patients receiving Anascorp had at least 1 adverse reaction.

Table 1.3 Adverse events occurring in clinical trials with Anascorp

Adverse event	**Number of patients who had AE [N=1534]** **n (%)**
Vomiting	72 (4.7)
Pyrexia	63 (4.1)
Rash	41 (2.7)
Nausea	32 (2.1)
Itching	31 (2.0)
Headache	29 (1.9)
Rhinorrhoea	28 (1.8)
Myalgia	25 (1.6)
Fatigue	24 (1.6)

Cough	22 (1.4)
Diarrheal	20 (1.3)
Lethargy	17 (1.1)

No patient died or discontinued participation in the study due to severe adverse reactions. Eight patients (0.5%) were considered affected by a condition of serum sickness (type III hypersensitivity); in no patient was a complete syndrome of serum sickness reported. Three patients were treated with systemic corticosteroids and another five received no treatment or received symptomatic treatment. There were 34 patients with a total of 39 severe adverse reactions such as respiratory distress, aspiration, hypoxia, ataxia, pneumonia, and eye swelling. It is unclear whether these adverse reactions were related to Anascorp, poisoning, or a combination of both factors (55-56).

Appendices hereto also include the Anascorp, BAT and Anavip package inserts, since they provide safety reference information on the Fab'2 fractions of equine immunoglobulins (57-61):

- **Anavip:** The most frequent adverse reactions (>2%) in clinical studies were: pruritus, nausea, rash, arthralgia, peripheral oedema, myalgia, headache, pain in extremities, vomiting and erythema. 24% (21/86) of the patients studied in clinical studies were 16 years of age or younger (6 patients were between 2 and 5 years of age, and 15 patients were between 5 and 16 years of age). None of the paediatric patients in the phase 3 study had a recurrent coagulopathic effect. None of the adverse reactions in paediatric patients were serious. The most common adverse reactions amongst paediatric patients were nausea and vomiting, itching, and fever. Therefore, safety and efficacy in the paediatric population did not differ from that observed in adults.

- **BAT:** The most common adverse reactions observed in ≥ 5% of healthy volunteers in clinical studies were headache, nausea, pruritus, and urticaria. The most common adverse reactions reported in ≥ 1% of patients in the context of a clinical study were pyrexia, rash, chills, nausea, and oedema.

- Post-marketing experience: the following hypersensitivity/allergic reactions have been reported in patients treated with BAT: anaphylactic shock; angioedema; urticaria.

- **Post-marketing experience with Anascorp:** chest tightness, palpitations, rash and pruritus.

- **FabenFlu:** In the phase 1 study, this F(ab')2 was well tolerated, and there were no deaths or serious adverse events (SAEs). Three patients had mild AE (1 each with blepharospasm, sinusitis, and pyrexia). The pyrexia event (38°C) was considered

probably related to the infusion and resolved after 37 min. Laboratory evaluations of blood and urine samples and physical examinations of heart rate, electrocardiographic readings, and body weight did not reveal any clinically significant safety concerns.

- An evaluation of the use of fixed-dose monovalent immunoglobulin G (equine) antivenin from *vipera palaestinae* was carried out for the treatment of the most venomous snakebite in Israel, in cases that occurred from March 2008 to March 2014 and cared for in two paediatric emergency departments. 57 patients between 1 and 17 years of age were evaluated. The antivenin was administered to 25 (42%) children who presented local and systemic reactions of moderate to severe intensity to the snakebite. None of these patients developed adverse reactions, serum sickness, or any other side effect to the antivenin.

1.3.4 F(ab')2 fraction of equine immunoglobulins - Phase 1 results with INM004

The safety data obtained from the phase 1 study (CT-INM0004-01) indicate that INM004 was well-tolerated. Table 1.4 presents complete information on AEs that occurred during human exposure to IMP. The AE considered possibly or probably related to the IMP by the investigator are presented in Table 1.5.

Table 1.4 CT-INM004-01 - Adverse events reported in each treatment arm, regardless of causality

Adverse event	Active treatment arm (n = 11)	Placebo arm (n = 3)
Headache	5 (45 %)[1]	0
Constipation	1 (9 %)	0
Pain in the site of extraction	1 (9 %)	0
Flushing	1 (9 %)	0
Worsening of plantar fascitis	1 (9 %)	0
Bruising in the site of extraction	2 (18 %)	0
Diarrhea	0	1 (33 %)
Anal irritation	0	1 (33 %)
Rhinitis	1 (9 %)	1 (33 %)
Earache	1 (9 %)	0

[1] Three (3) AE correspond to the same subject.

Table 1.5 CT-INM004-01 - Adverse events reported with a possible or probable causal relation to the investigational medicinal product

Subject code	Treatment arm assigned	Dose	Body weight (kg)	Total dose (mg)	Sex	Age	Ethnicity	Adverse events	Relationship/causality
3231-16	INM004	3 repeat doses 4 mg/kg	69.9	838.8	Female	23	Hispanic	Flushing	Possibly related
								Headache	Possibly related
3231-18	INM004	3 repeat doses 4 mg/kg	57.2	686.4	Female	50	Hispanic	Headache (mainly frontal)	Probably related
								Frontal headache	Probably related
3231-23	INM004	3 repeat doses 4 mg/kg	67.1	805.2	Female	23	Hispanic	Rhinitis	Possibly related

Two subjects had headache; this AE was assessed as possibly or probably related to the study drug in both cases. The occurrence of the headache event was not associated with the infusion or any other activity carried out during the study.

One subject developed mild flushing lasting 1 minute at the beginning of the 1st. infusion. The reaction stopped spontaneously and required no treatment. This reaction was rated as possibly related to the study drug.

One subject presented moderate rhinitis with full recovery (restoration of the original state). This case is included within the adverse reactions at the investigator´s judgement, and was classified as an event possibly related to the investigational product; for INMUNOVA, it was not possible to determine the existence of a causal relationship with the study drug.

Analysis of the distribution of AE amongst the subjects indicated that 2 AE (mild headache and flushing events) occurred in 1 subject; the headache event occurred twice in another subject, and rhinitis was a single event that occurred in a 3rd subject.

There were no serious and unforeseen adverse drug reactions upon application of the product in humans, and no SAEs have been reported. Adverse reactions are listed in Table 1.6, ordered by System Organ Class (SOC). All the reported events were non-serious, as were the adverse events that are presented in Table 1.4.

Table 1.6 CT-INM004-01 - Adverse events reported by System Organ Class (SOC)

System Organ Class (SOC)	Adverse event	Number of subjects	Serious (yes/no)	Number of events
General disorders and administration site conditions	Flushing	1	No	1
Injuries and poisoning	0	0	0	0
Nervous system disorders	Headache	2	No	3
Skin and subcutaneous tissue disorders	0	0	0	0
Gastrointestinal disorders	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	0
Infections	0	0	0	0
Respiratory, thoracic and mediastinal disorders	Rhinitis	1	No	1
Immune system disorders	0	0	0	0
Vascular disorders	0	0	0	0
Psychiatric disorders	0	0	0	0
Eye disorders	0	0	0	0
Haematological and lymphatic disorders	0	0	0	0
Hepatobiliary disorders	0	0	0	0
Renal and urinary disorders	0	0	0	0
Cardiac disorders	0	0	0	0
Pregnancy, postpartum and perinatal disorders	0	0	0	0
Ear and labyrinth disorders	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0

Social circumstances	0	0	0	0
Benign, malignant and unspecified neoplasms (including cysts and polyps)	0	0	0	0
Reproductive system disorders	0	0	0	0
Endocrine disorders	0	0	0	0
Medical and surgical procedures	0	0	0	0
Birth defects and genetic disorders	0	0	0	0
Others	0	0	0	0

- Table 1.4 shows the AE that occurred in the treated group versus the group that received placebo, with their incidence %. The AE listed do not necessarily have a causal relation with the IMP. The latter are presented in Table 1.5 A subject may have presented more than one event, or the same event on more than one occasion.

1.3.4.1 General considerations related to the safety of CT-INM004-01

- There were 14 non-serious AE (Table 1.4), mild to moderate intensity, none severe. Those possibly or probably related to the medication are headache, predominantly frontal, and flushing (Table 1.5). Headache occurred in 3 of 11 subjects in the active treatment arm and in 0 of 3 subjects in the placebo arm, all of them in stage II; this represents a prevalence of 27%, a value that is not definite and that could be modified during phase 2.

- Changes in laboratory and physical examination parameters are not considered clinically significant. There were no cardiovascular or haematological events.

- IMP was well tolerated.

- There were no adverse events of special interest (AESI), such as hypersensitivity or immunogenicity reactions. These reactions are frequently observed in response to infusion of biological products and were therefore considered “of special interest”.

It was concluded that the presence of headache is an AE that could be related to the investigational product. It could be an adverse event of the class, in accordance with the events that have occurred for other similar F(ab’)2 drugs. The presence of other observations of safety events has not been detected at any time during the study.

1.3.5 F(ab')2 fraction of equine immunoglobulins - Phase 2/3 results with INM004

At the end of the evaluation period in May 2020 of the study CT-INM004-02 (*Double-blind, placebo-controlled, adaptive, Phase 2/3 study, to evaluate the pharmacokinetics, safety and efficacy of INM004 in paediatric patients with diarrhoea Bloody Shiga toxin positive for the prevention of Haemolytic Uremic Syndrome*) a total of 11 patients had been randomised. Of these, two patients received only the first dose of the investigational product due to withdrawal of consent (patient AR01-001) and due to non-compliance with study entry criteria (patient AR08-004), while seven patients received full treatment of the study (blinded).

25 non-serious AE were reported out of a total of ten patients Table 1.7. Only three of them (mild "headache" [patient AR05-001] and two reports of mild "rhinitis" [patients AR08-001 and AR08-003] were listed (expected) AE. The investigator considered the following AE as possibly related to the administration of the investigational product: "morbiliform allergic rash" (AESI, patient AR01-001), "neutropenia" (SAE, patient AR08-002), "mild afebrile rhinitis" and "rhinorrhoea" (non-serious AE, patient AR08-003). Furthermore, the AE "vomiting" (non-serious AE, patient AR06-001) was considered related to the underlying disease of the study.

One AE occurred within 24 h after the administration of the 1st. dose of the investigational product (“rhinorrhoea” [patient AR08-003] and three AE occurred on the same day as the 2nd infusion of the investigational product (“fever” [patient AR05-003], “increased LDH” [patient AR08-003] and “neutropenia” [patient AR08-002]).

Two cases of neutropenia were reported, one of them was evaluated as serious AE (patient AR08-002, described above) and possibly related to the administration of the investigational product (Table XX) and the other referred to a non-serious neutropenia (patient AR08-001) evaluated as not related to the investigational product, but related to recent exposure to routine vaccination (Sabin + pentavalent + chickenpox vaccines). No therapy was performed for these AE and the subjects made a full recovery.

Results of physical examination, laboratory data, vital signs, and ECG evaluations revealed no safety-relevant findings. No unblinding was performed due to emergency/therapeutic reasons. At the time of this report, no patient developed haemolytic uremic syndrome.

The benefit risk profile remains favourable for the investigational product.

Table 1.7- CT-INM004-02 List of SUSARs

Subject ID	AE term (according to the investigator)	Seriousness criteria	System Organ Classification (MedDRA SOC)	Preferred term (MedDRA PT)	Start date	Country of occurrence	Medical assessment
AR08-002	**Neutropenia**	**Others (medically important event due to sudden drop in neutrophil count)**	**Blood and lymphatic system disorders**	**Neutropenia**	**16/01/2020**	**Argentina**	Female patient who developed a decrease in neutrophil count from baseline (-27% in 24-h, nadir: -71% in approximately 48 h) after infusion of the 1st. dose of the investigational product. The patient had no fever or other complications associated with neutropenia and had a rapid improvement in neutrophil count. As possible confounding factors, although an association between the underlying positive STEC infection and decreased neutrophil count is unlikely, this cannot be ruled out. In addition, the patient had received midazolam (intranasal) and chloral hydrate a few minutes before the start of the infusion of the investigational product (blinded) and due to the patient's concern. Although the search in the scientific literature did not show evidence of an association between the use of midazolam and/or chloral hydrate and the development of haematological adverse reactions, a causal relationship cannot be ruled out at this time. However, an association of the event with these drugs is considered unlikely. A class effect cannot be established, as no safety data were found on haematological involvement with respect to the use of similar F(ab')2 drugs (e.g. equine sera such as tetanus toxin, antivenin, or arachnid serum). From the assessment of the principal investigator and the consulted external haematologist, at this point it is not possible to establish a clear causal relationship. The patient did not develop haemolytic uremic syndrome. The risk-benefit profile continues to be favourable for the investigational product.

Table 1.8- CT-INM004-02 LIST OF ADVERSE EVENTS

Subject number	Randomisation date	Name of adverse event	Start date	End date	Serious	AESI	Outcome	Action taken with the study medication	Other measure taken	Causal relation with the investigational product (investigator)	Relation with the other treatment	Severity
AR01-001	2020-01-29	MORBILIFORM ALLERGIC RASH	01/02/2020	01/02/2020	No	Yes	Recovered	Not applicable	Medication needed	Possibly related	Other medical condition	Mild
AR05-001	2019-10-22	VULVITIS	UNK/11/2019	21/11/2019	No	No	Recovered	Not applicable	No	Not related	No	Mild
AR05-001	2019-10-22	PARASITOSIS	18/12/2019		No	No	Not recovered	Not applicable	Other	Not related	No	Mild
AR05-001	2019-10-22	HEADACHE	22/12/2019	22/12/2019	No	No	Recovered	Not applicable	Medication needed	Not related	No	Mild
AR05-002	2020-01-15	LARYNGITIS	13/02/2020	16/02/2020	No	No	Recovered	Not applicable	Medication needed	Not related	No	Mild
AR05-002	2020-01-15	BRONCHOSPASM	29/02/2020	06/03/2020	No	No	Recovered	Not applicable	Medication needed	Not related	Other medical condition	Mild
AR05-003	2020-01-21	FEVER	22/01/2020	22/01/2020	No	No	Recovered	Dose not modified	Medication needed	Not related	No	Mild

Subject number	Randomisation date	Name of adverse event	Start date	End date	Serious	AESI	Outcome	Action taken with the study medication	Other measure taken	Causal relation with the investigational product (investigator)	Relation with the other treatment	Severity
AR05-003	2020-01-21	CUT ON THE CHIN	27/01/2020	05/02/2020	No	No	Recovered	Not applicable	Other	Not related	No	Mild
AR06-001	2019-10-24	VOMITING	26/10/2019	26/10/2019	No	No	Recovered	Not applicable	No	Not related	Study disease	Mild
AR06-001	2019-10-24	TONSILITIS	14/11/2019	22/11/2019	No	No	Recovered	Not applicable	Medication needed	Not related	No	Moderate
AR08-001	2019-12-30	NEUTROPENIA	27/01/2020	29/01/2020	No	No	Recovered	Not applicable	No	Not related	No	Moderate
AR08-001	2019-12-30	COMMON COLD	UNK/01/2020	UNK/01/2020	No	No	Recovered	Not applicable	No	Not related	No	Mild
AR08-001	2019-12-30	LARYNGITIS	19/02/2020	UNK/UNK/2020	No	No	Recovering	Not applicable	Medication needed	Not related	No	Moderate
AR08-002	2020-01-15	NEUTROPENIA	16/01/2020	20/01/2020	Yes	No	Recovered	Dose not modified	No	Possibly related	No	Severe
AR08-002	2020-01-15	FEVER	01/02/2020	01/02/2020	No	No	Recovered	Not applicable	Medication needed	Not related	No	Mild
AR08-002	2020-01-15	UPPER RESPIRATORY TRACT COLD	01/02/2020	01/02/2020	No	No	Recovered	Not applicable	Medication needed	Not related	No	Mild

Subject number	Randomisation date	Name of adverse event	Start date	End date	Serious	AESI	Outcome	Action taken with the study medication	Other measure taken	Causal relation with the investigational product (investigator)	Relation with the other treatment	Severity
AR08-003	2020-01-31	LDH INCREASED	02/02/2020	28/02/2020	No	No	Recovered	Dose not modified	No	Not related	No	Mild
Subject number	**Randomisation date**	**Name of adverse event**	**Start date**	**End date**	**Serious**	**AESI**	**Resolution**	**Action taken with the study drug**	**Other measure taken**	**Causal relation with the investigational product (investigator)**	**Relation with the other treatment**	**Severity**
AR08-003	2020-01-31	RHINORRHOEA	01/02/2020	01/02/2020	No	No	Recovered	Dose not modified	No	Possibly related	No	Mild
AR08-003	2020-01-31	MILD AFEBRILE RHINITIS	06/02/2020	09/02/2020	No	No	Recovered	Not applicable	No	Possibly related	No	Mild

1.3.6 Clinical development plan

INMUNOVA plans to bring COVID-19 treatment directly into phase II/III trials, bypassing phase I and preclinical trials due to previous experience and safety data that have been obtained from Shiga antitoxin (INM004), as well as other similar F(ab) for other indications like botulism, snake and scorpion poisoning as explained above. COVID-19 infection is a serious and life-threatening condition that has become a pandemic, for which there is no drug for prevention or treatment. The proposed drug INM005 represents a potentially important advance, so we believe that it is desirable that there are no unnecessary delays to the start of the phase II/III study in the target population.

1.4 Dose selection

The dosage regime of INM005 planned for use in this clinical study are 2 doses of 4 mg/kg, administered 2 times approximately 48 h (± 2 h) apart. The selection of the exposure level is based on preclinical *in vitro* data related to the seroneutralisation assay performed with SARS-CoV-2, clinical data on the levels of neutralising antibodies supplied in convalescent plasma, as well as PK of INM004 obtained from the phase 1 study (CT-INM004-01) in healthy adult volunteers.

1.4.1 Dosage rationale

In the phase 1 clinical study (CT-INM004-01), carried out in Argentina with 14 healthy adult volunteers (of both sexes), the safety, tolerance and PK of INM004 were evaluated. This study was divided into 2 stages; in stage I, patients in cohort I received a single dose of INM005 of 2 mg/kg and patients in cohort II received a single dose of INM005 of 4 mg/kg. After an interim analysis, stage II involved three doses of INM004 of 4 mg/kg administered every 24 hours (i.e., at t=0 h, 24 h, and 48 h). INM004 plasma concentrations for PK analysis were obtained at predefined time points over 7 days (plus a final sample obtained at 30 days) from the 1st. dose of INM004.

The product INM005 is manufactured using the same technological platform and the same manufacturing plant used to obtain Shiga anti-toxin (INM004) throughout its development. Both molecules correspond to the fraction F(ab')2 of hyperimmune equine immunoglobulin, in one case anti-Shiga toxin and in the other anti-SARS-CoV-2, so they are indistinguishable

from a physicochemical point of view. Added to this, within a hyperimmune serum, no more than 10% of the immunoglobulins correspond to those specific against the antigen of interest, so no variation is expected in the PK of both products. All the same, a PK study is planned to be carried out in this protocol to corroborate these assumptions. Therefore, priority was given to define a dosage that ensures an administration of a quantity of neutralising antibodies for SARS-CoV-2 greater than the convalescent plasma and that at the same time are present in the body for at least 8 days.

1.4.2 Assumptions

- The i.v. (mg/kg) and peak serum concentrations (ng/ml) of INM005 after administration of a single dose are proportional. In other words, immediately after i.v. injection, the total amount of INM005 is diluted in the patient's blood and reaches the maximum concentration, within the dose range of INM005 studied; higher doses lead to larger peaks whose increase is roughly proportional.

- There is a very high probability that moderate to severe illness will develop within 7 days after symptoms begin. It is very difficult to accurately estimate the amount of virus present in the body as this depends on many factors such as inoculum size and type of host.

- It is intended to maintain the concentrations of the product for at least 8 days to control the entry of the virus into the cells and prevent its spread.

- <u>Comparison between the neutralising power of convalescent plasma vs the chosen dose of INM005</u>

  A Neutralising Unit (NU) is defined as the inverse of the neutralising titre in a validated serum neutralisation assay.

Convalescent plasma

Average titre 1:200 equals 200 NU/ml

Average transfusion volume 200 ml

The dose is around **40,000 NU** per patient, regardless of the patient's weight.

<u>INM005</u>

Average titre 1:10,000 equals 10,000 NU/ml

Two doses of 4 mg/kg spaced by 48 h

For an individual weighing 80 kg, two doses of 10.67 ml would be injected, total 21.33 ml

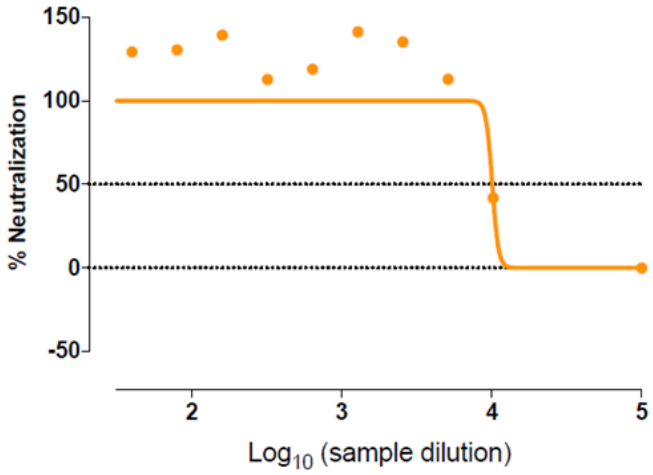
The dose is **213,333** NU for a patient of this weight, being **more than 5 times higher** than the neutralising power of average plasma.

- The planned dosage of INM005 is intended to obtain, at the maximum concentration peak, concentration levels of INM005 that would have the ability to neutralise the virus, with a higher potency than convalescent plasma as demonstrated in the seroneutralisation tests in vitro.

1.4.3 Preclinical data

The potency of INM005, that is, the neutralising capacity of INM005 for infection with SARS-CoV-2, was tested in independent laboratories (Respiratory Diseases Service of INEI-ANLIS Malbrán; Instituto de Virología "Dr J. M. Vanella"; Laboratorio COVID-19 Facultad de Ciencias Médicas, National University of Córdoba, and Centre for Research in Animal Health (CReSA) - IRTA- Campus of the Autonomous University of Barcelona. Briefly, in this assay, serial dilutions of INM005 were made and SARS-CoV-2 is used to infect a monolayer of the VERO cell line and the titre is determined by means of the reduction of plaque-forming units (PFU), TCID50 (Median Tissue Culture Infectious Dose). In all cases, the neutralising antibody titre was higher than 1:10,000, while convalescent plasma [AIM2].

Figure 1.4 As an example, the seroneutralisation analysis carried out at the Centre de Recerca en Sanitat Animal (CReSA) is shown as Log10 of the dilution of the sample vs. % of neutralisation.



1.4.4 Phase 1 study

A phase 1 study with INM004 has been completed in Argentina (Protocol No. CT-INM004-01). A total of 14 volunteers enrolled; 3 volunteers received 2 mg/kg of INM004, 3 volunteers received 4 mg/kg of INM004, 5 volunteers received 3 doses of 4 mg/kg 24h apart, and 3 volunteers received placebo.

The PK data obtained from the 8 healthy volunteers in a single dose cohort can be summarised as follows:

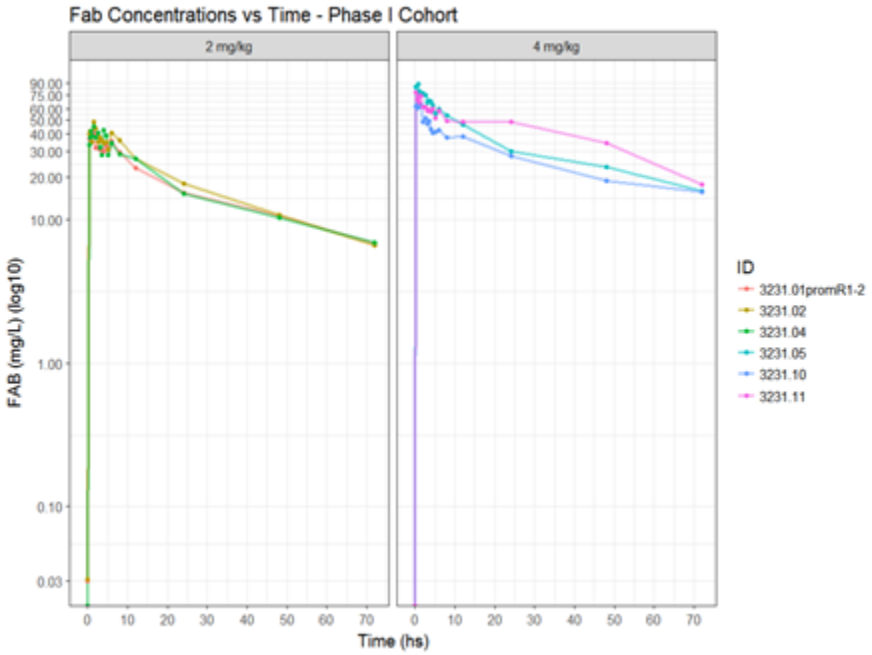
- A total of 19 samples were obtained for each volunteer for antitoxin PK measurements, after the completion of the 50 min infusion of INM004. (Sample collection times: 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 3, 3.5, 4, 4.5, 5, 6; 8, 12, 24, 48 and 72 h). INM004 concentrations were quantified using the ELISA method.
- Terminal half-lives of INM004 (lambda z) after a single dose were relatively long, with a median of 41.24 h (range 33.19-52.92 h).
- The peak concentrations of INM004 (maximum observed concentrations, C_{max}) had a median value of 45.14 mg/L (range: 41.76-48.11 mg/L) for the volunteers who were administered the dose of 2 mg/kg and 77.70 mg/L (range 64.8-88.4 mg/L) for those to whom the 4 mg/kg dose was administered.
- The area under the concentration versus time curve extrapolated to infinity (AUC0-inf) had a median of 1557.82 mg * h/L for the volunteers who received 2 mg/kg and 3496.34 mg*h/L for those who received 4 mg/kg. The increase in $AUC_{0\text{-}inf}$ was

basically proportional to the dose of INM004 administered. The dose-normalised $AUC_{0\text{-}inf}$ had a median value of 11.84 mg*h/L for each mg of INM004 administered (range: 7.29-14.84 g*h/L/mg).

- The Volume of distribution (Vd) of the terminal phase had a median value of 4.73 L (range: 4.22-8.81 L). The median Vd corrected for body weight was 77 ml/kg (range: 52-89 ml/kg), which suggests a predominantly intravascular distribution of the product.
- The clearance (clearance, Cl) observed had a median value of 84 ml/h (1.41 ml/min) and a range between 67 and 137 ml/h (1.12-2.29 ml/min).
- There is a biphasic elimination profile compatible with a two-compartment model.

This is summarised in Figure 1.5

Figure 1.5 Concentration of INM004 over time in 6 volunteers of the Phase 1 study (3 volunteers received 2 mg/kg, 3 volunteers received 4 mg/kg) - Logarithmic scale

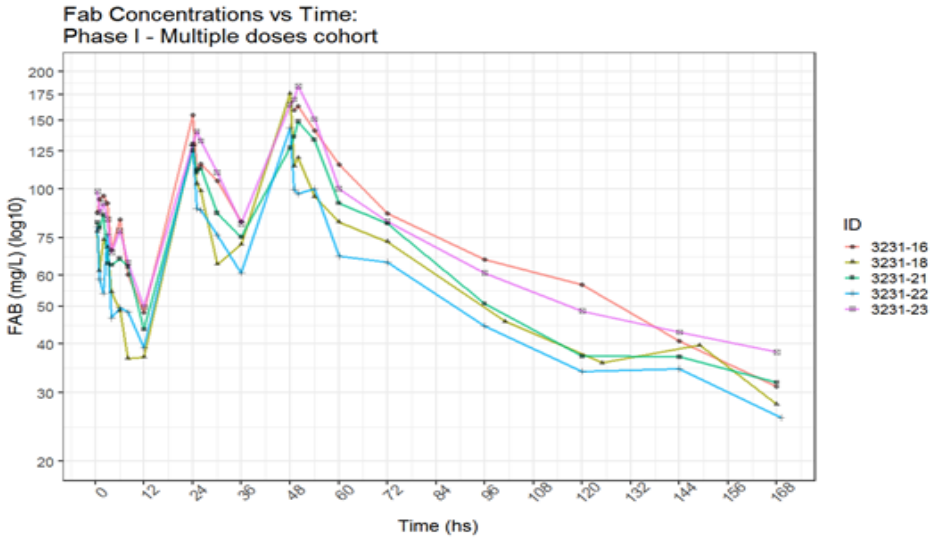


Abbreviations: h, hours

The non-compartmental analysis (NCA) of INM004 concentrations for the **repeated dose cohort (N=5)** yielded the following results (see Figure 1.6), which was consistent with the results obtained for the administration of single doses of INM004:

- The estimated terminal half-lives after the third dose of INM004, using at least 3 plasma concentrations of INM004, (lambda z) were relatively long, with a median value of 68.6 h (range of 55.3-137 h). These observed half-lives were longer than those observed after a single dose of INM004, in the 1st. cohort of the phase 1 study. These differences could be due to some degree of saturation of the mechanisms of elimination of INM004 after the administration of repeated doses. However, these changes appear of relatively limited relevance in the context of the few doses of INM004 that are required (i.e. 1 or 2 doses of INM004), as proposed for the treatment regimen. On the other hand, in the event that a larger quantity of INM004 doses should be administered, it seems likely that it is possible to expect an accumulation of INM004, at levels higher than those suggested by the estimated half-lives after administration of INM004 in single doses.
- The C_{max} at the end of the third infusion of INM004 had a median of 175.7 mg/L (range 143.5-200.9 mg/L).
- The C_{max} observed after the first infusion had a median value of 85.7 mg/L (range: 77.8-98.6 mg/l, similar to that observed previously in volunteers who received only a dose of 4 INM004 mg/ kg (median C_{max} of 77.7 mg/l for INM004 single dose study above); the C_{max} observed after the second infusion of INM004 had a median value of 130.1 mg/l (range 125.5-155 mg/l).
- The median area under the concentration versus time curve, extrapolated to infinity, (AUC_{inf}) for the total amount administered of 3 doses of INM004 (total cumulative dose of INM004: 12 mg/kg divided into 3 doses of INM004, 4 mg/kg each, spaced by a period of 24 h, t=0 h, 24 h and 48 h) was 14,121.98 mg*h/L (range 12426.61-20198.89).
- The dose-normalised AUC_{inf} had a median value of 18.73 mg*h/L for each mg of INM004 (range 15.62-25.09 mg*h/L/mg for each mg of INM004). Median dose-normalised AUC_{inf} was 58% higher than in the previous INM004 single dose study (dose-normalised median AUCinf in INM004 single dose study: 11.84 mg*h/L for each mg of INM004, range 7.29-14.84), supporting the suggested possibility that the clearance rate of INM004 is reduced after the administration of multiple doses.
- The median volume of distribution (Vd) was 5.26 L (range 4.27-7.88 L), similar to the value previously observed after a single dose of INM004. The median Vd corrected for body weight was 84 ml/kg (range 61-117 ml/kg), consistent with a predominantly intravascular INM004 distribution.
- The median clearance (Cl) was 53 ml/h (0.88 ml/min), with a range between 40 and 64 ml/h (0.66-1.06 ml/min). The median CL with correction for body weight was 0.85 ml/h/kg (range: 0.59-0.96 ml/h/kg).

Figure 1.6 Concentration of INM004 over time (logarithmic scale)



Abbreviations: hs = hours

The pharmacokinetics of INM004 after 3 doses spaced 24 h apart did not differ significantly from what had already been observed in the single dose study of INM004. However, a moderate accumulation of INM004 was observed, beyond that expected based on the PK observed in the INM004 single dose study. This accumulation (resulting from the lower clearance observed after administration of repeated doses) is not expected to significantly affect the anticipated exposure in view of the administration regimen proposed to date (i.e., single dose or 2 doses of INM004). On the other hand, if a larger number of doses is used, the potential for disproportionate accumulation of dose (due to reduced clearance with the administration of multiple doses) should be considered when making a decision regarding the dosages dose of INM004 to be administered.

The INM004 levels observed after the 2nd dose (median C_{max} of 130.1 mg/L) were close to the levels that, as predicted, would be recorded after the administration of 2 doses (predicted based on the behaviour of PK in the single dose study).

1.4.5 Extrapolation of kinetic data at planned doses for INM005

From a population pharmacokinetics model (63-64) using as a basis the PK data obtained from the phase 1 trial for INM004 (CT-INM004-01), different dosage schedules and PK for

INM005 were simulated. This type of model works very well since the study population and the product are similar to that of phase 1.

The simulations were done assuming doses of 4 mg/kg in patients of 70 kg. The curves represent the population median concentration, with the 90% confidence interval. Five hundred simulations of the entire population of 11 volunteers obtained from the CT-INM004-01 trial were performed. The pharmacokinetics model is made in Monolix (62), 2019R2, and the simulations and graphs in R, with the Simulx package. This is a bi-compartmental population pharmacokinetics model, and the parameters are V1 (central volume of distribution), Cl (elimination constant, indicates excretion from the central compartment to the "outside", V2 (peripheral volume, e.g. tissues, extravascular water, lymph, etc.), and Q (clearance to and from the peripheral volume). The model assumes that it is eliminated from the central compartment, that is, there is no elimination from V2 and therefore what goes from V1 to V2 at some point returns to V1. The infusion enters compartment 1, which has volume of distribution V1, it is distributed to compartment 2, which has volume of distribution V2. The passage from compartment 1 to 2 (and vice-versa) has a "speed" Q. Finally, the drug is eliminated from compartment 1 with a "speed" Cl (see figure). The population distribution gives a statistical variability to the parameters, with a distribution (logNormal). The statistical model (residual error l) takes into account a combined error (proportional + fixed residual error), the residual error being low. The V2 is influenced by weight.

Figure 1.7 Bicompartmental population pharmacokinetics model scheme.

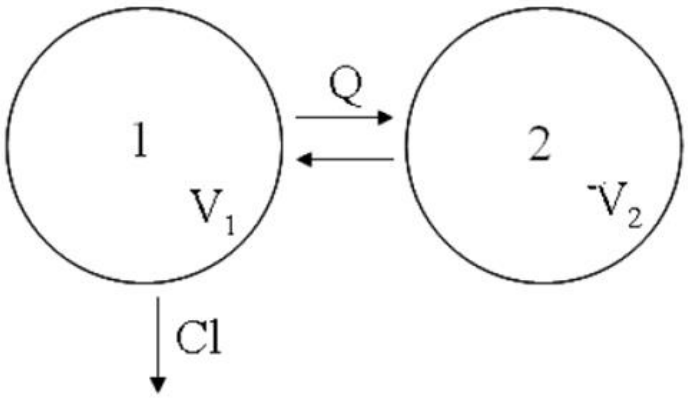


Table 1.9 Simulation parameters

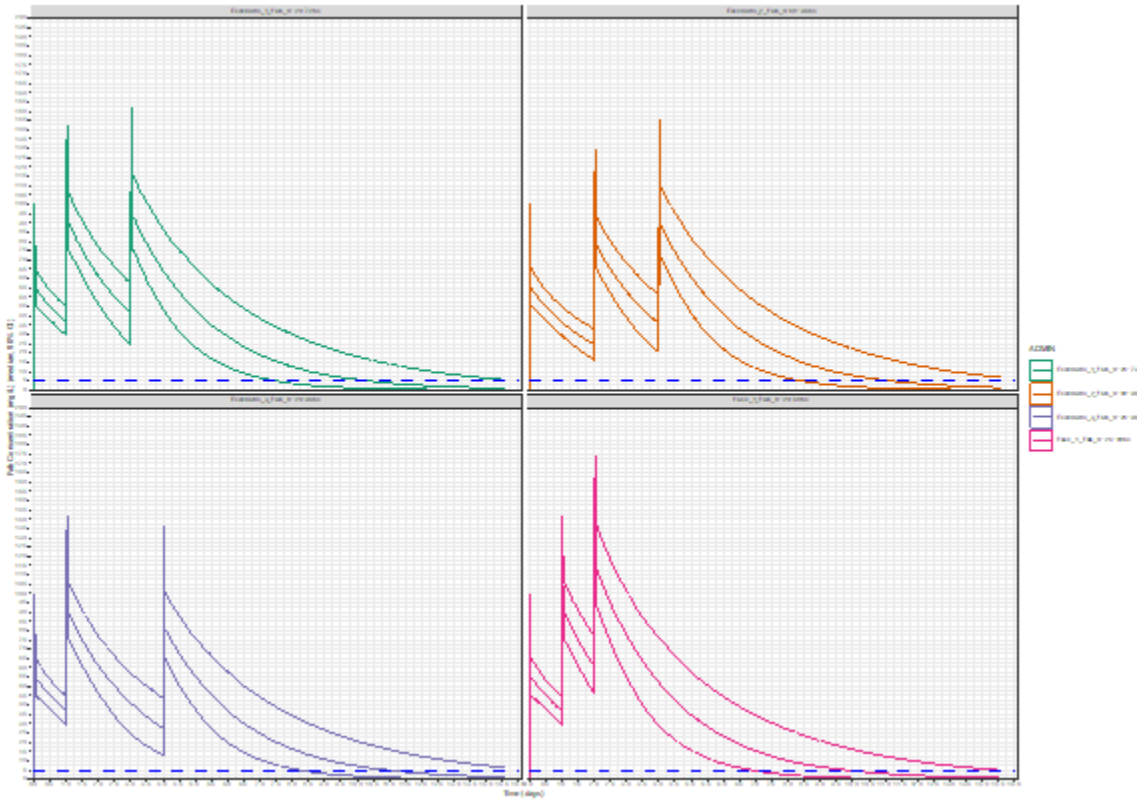
CI pop	0.071976554800018
V1 pop	0.447770889301066
Q pop	6.03570568981478
V2 pop	0.849574567795506
Beta V2 WT	0.0214472765523809
Omega Cl	0.252701314813687
Omega V2	0.0306518348168635
Fixed error (a)	0.143635819360993
Proportional error (b)	0.173797848707843

Different dosage schedules were simulated taking into account 2 and 3 administrations of 4 mg/kg.

For 3 administrations the following times were simulated:

- t=0h; t= 24h and t=72h
- t=0h; t= 48h and t=96h
- t=0h; t= 24h and t=96h
- t=0h; t= 24h and t=48h

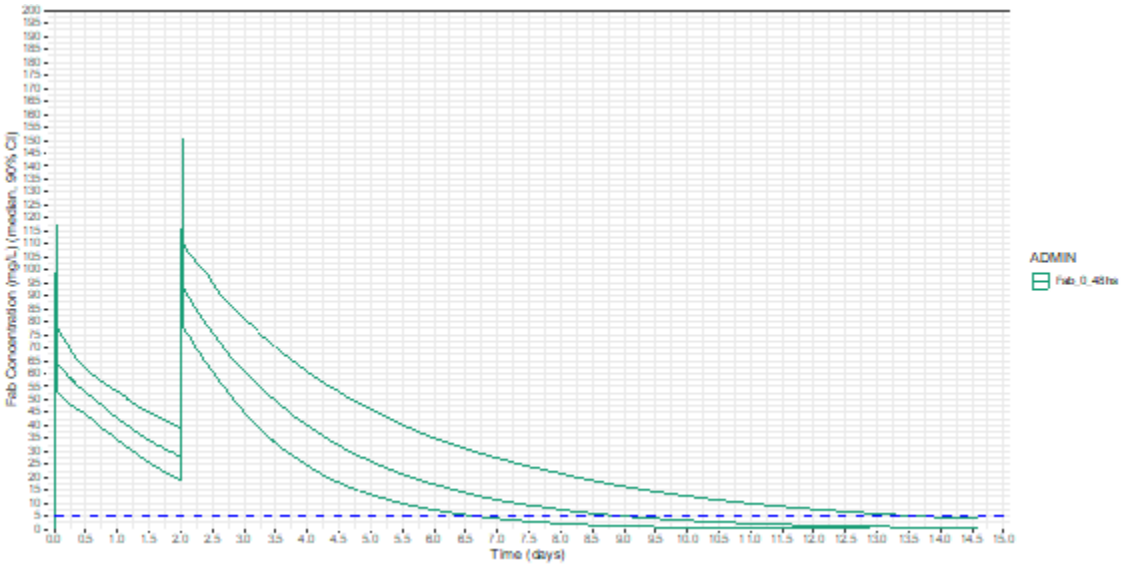
Figure 1.8 Simulations of INM005 concentrations over time (3 administrations)



For two administrations the following were simulated:

t=0h and t=48h

Figure 1.9 Simulation of INM005 concentration over time (2 administrations)



Taking into account the results obtained in the simulations, the scheme of two administrations spaced by an interval of 48 h was chosen as it minimizes the number of infusions, and a permanence of the investigational product is obtained at concentrations compatible with the neutralisation of the virus up to 9 days on average.

1.4.6 Future pharmacokinetics measurements

The PK profile of INM005 in the study population will be evaluated in a sub-study with 20 subjects. A blood sample will be drawn from subjects for PK tests immediately before the 1st. administration of the study drug, at the end of the 1st. administration of the study drug, 24 h after the 1st. administration of the study drug, immediately before the 2nd administration of the study drug, at the end of the 2nd administration of the study drug, 24h after 2nd study drug administration and 7 days after 1st. study drug administration. Whenever possible, an opportunistic sampling approach will be implemented (that is, samples will be obtained from the remnant of blood obtained for routine clinical evaluation of the patient, which will avoid additional venipuncture and minimize exposure of the health staff).

2 STUDY OBJETIVE

2.1 Primary

The primary objective of the study is:

Demonstrate the efficacy and safety of INM005 in COVID-19 in terms of clinical improvement 28 days after the start of treatment with the investigational product.

2.2 Secondary

The secondary objectives of the study are:

1) Assessment of the pharmacokinetics of INM005

2) Assessment of efficacy in terms of time to disease progression

3) Assessment of efficacy in terms of disease progression

4) Assessment of efficacy in terms of change in viral load

2.3 Exploratory

The exploratory objectives of the study are:

1) Assessment of anti-SARS-CoV-2 antibodies levels

2) Evaluation of the change in laboratory variables and other markers related to the immune response and inflammation that can be identified as possible factors of progression of COVID

3) Assessment of immunogenicity at 28 days

3 STUDY ENDPOINTS

3.1 Primary

Primary efficacy endpoint:

The proportion of patients that showed improvement 28 days after the administration of the first dose will be determined. A responder subject is defined as a subject with an improvement in at least 2 categories in the 8-point WHO clinical status ordinal scale (Section 7.1) or with hospital discharge.

Safety endpoints:

The incidence of related adverse events and of adverse events of special interest during the study period

3.2 Secondary

1) Concentration of product INM005 in serum at different times after administration of treatment

2) Time to improvement in at least 2 categories in the 8-point WHO clinical status ordinal scale

Time to discharge (days)

Time to discharge from ICU (days)

3) Proportion of patients who show an improvement in at least 2 categories in the 8-point WHO clinical status ordinal scale 7 and 14 days after the start of the treatment

Proportion of patients with hospital discharge at 28 days

Proportion of patients who required admission into ICU up to Day 28

Proportion of patients who required MRA up to Day 28

Proportion of patients who died up to Day 28

4) Changes in viral load from baseline to 7 days and 21 days after starting treatment

3.3 Exploratory

The following exploratory endpoints will be evaluated in all subjects:

· To be carried out by a central laboratory

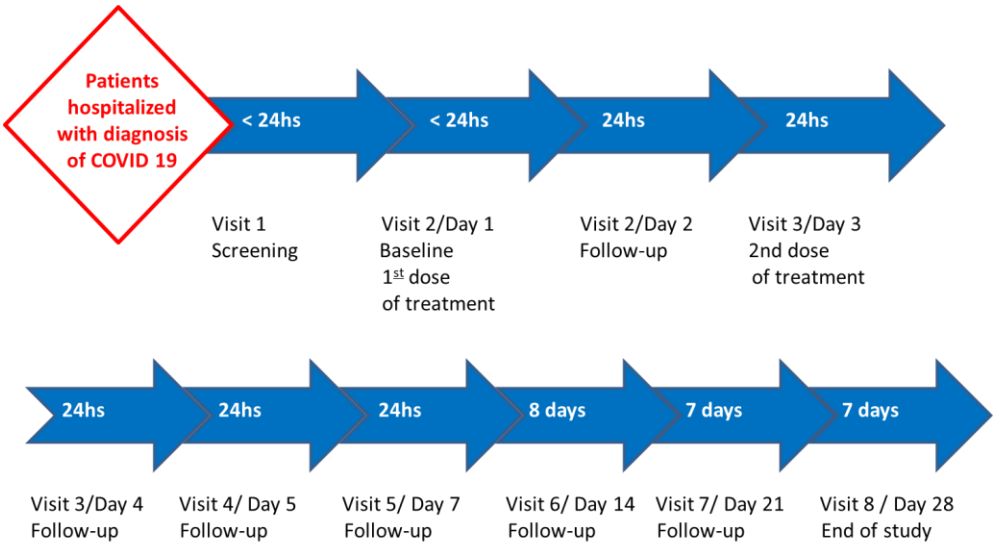
1. Measurement of anti- SARS-CoV-2 antibody titres: IgG (0, 21 days)
2. Evaluable laboratory variables at baseline, 7 and 21 days: Troponin T, D-dimer, ferritin, LDH, C-reactive protein or other clinically relevant markers related to immune response and inflammation that can be identified as possible factors of progression of COVID
3. Measurement of anti- product INM005 antibodies: baseline and 21 days

4 STUDY PLAN

4.1 Study design

Phase II/III, randomised, double-blind, parallel group study, with an adaptive study design. The interim analysis will be performed in a "blinded" manner and, based on the rate of events in the control group, the futility of the treatment, the feasibility of the study, or the sample size will be adapted (73).

4.2 Schematic representation of the study



Randomisation

Ratio 1:1 **(INM-005: placebo)**

Staggered enrolment will be done for the first 12 subjects in 6:6 blocks.

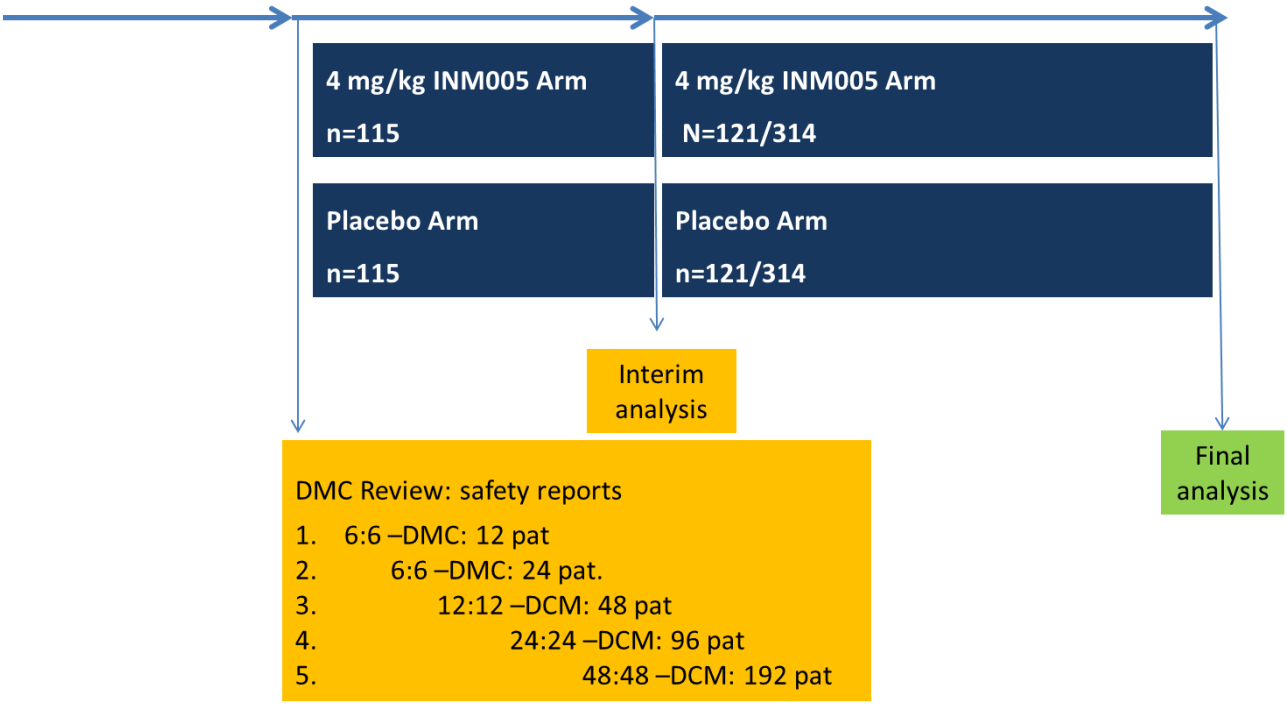
Randomisation will continue with a 1:1 ratio for each sub-cohort:

Treatment regime

Active 2 4 mg/kg INM005 doses (first dose visit 2/Day 1 and second dose Visit 4/Day 3)

Placebo

4.3 Study design scheme



A staggered recruitment of the first 12 subjects will be performed in 6:6 blocks. Randomisation will be carried out maintaining a 1:1 ratio in each sub-cohort:

- active treatment regime [two 4 mg/kg doses of INM005]
- placebo

Intensive monitoring will be done during this stage.

After the first 6 subjects have been recruited and 24 h post treatment have passed after the second dose, the Sponsor's Medical Monitor will review the safety data for this acute phase and report the safety findings.

This assessment will be repeated for the 2 blocks of 6 subjects each.

Any safety findings will be notified immediately to the Sponsor, DMC and Regulatory Agency, as established in current regulations.

The monitoring details will be specified in the Study Pharmacovigilance Plan, which will be finalised before the recruitment of the first patient into the study begins.

When the recruitment of the first 12 patients is complete, the DMC will review the safety data and inform whether the staggered recruitment should continue.

All DMC reports will be duly notified to the ANMAT.

4.4 Schedule of assessments

The procedures that will be carried out throughout the study are detailed in the Evaluation Schedule provided below. A detailed description of each assessment is provided in Section 6.2.

Visit	**V1**	**V2**		**V3**		**V4**	**V5**	**V6**	**V7**	**V8**
Time from the 1st. dose of study drug	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**[25]	**Day 7**[25]	**Day 14**[25]	**Day 21**[25]	**Day 28**[25]
Study procedures	Screening visit[1]	**Treatment phase** Baseline visit Dose 1[2]		Dose 2[2]	Follow-up visit	Follow-up visit	Follow-up visit	Follow-up visit	Follow-up visit	End of study visit
Location of visit	Hospital[3]					Hospital/outpatient				
Window		≤ 24 h from V1	24 h ± 2 h from first dose	≤ 24 h ± 2 h from Day 2	24 h ± 2 h from last dose	± 1 day	± 1 day	±2 days	±2 days	± 2 days
Review of results PCR diagnosis	X[5]									
IA/CF	X[5]									
Demographics	X									
Medical history/underlying diseases[4]	X									

Visit	V1	V2		V3		V4	V5	V6	V7	V8
Inclusion /Exclusion criteria	X	X[6]								
COVID history and symptoms[18]	X	X	X	X	X	X	X	X	X	X
Physical exam[7]	X	X[17]								
Height[7]	X									
Body weight[7]	X[7]	X[17]								
Vital signs[8]	X[9]	X[10]	X[10]	X	X	X	X	X	X	X
Oxygen saturation	X	X	X	X	X	X	X	X	X	X
ECG	X									
Haematology[11]	X[12]		X[9]		X[9]				X	
Serum biochemistry[13]	X[12]		X[9]		X[9]				X	
Pregnancy test	X[14]									
X-rays or chest CAT[26]	X									

Visit	V1	V2		V3		V4	V5	V6	V7	V8
Classification by WHO scale[15]	X	X[17]	X	X	X	X	X	X	X	X
Randomisation[16]		X								
Blood samples for viral load[19]		X					X		X	
Blood samples for biomarkers and future analysis[20]		X					X		X	
Blood samples for immunogenicity and anti-SARS-CoV-2 antibodies[20]		X							X	
Administration of study drug		X		X						
Evaluation of hypersensitivity reactions		X	X	X	X	X	X	X	X	X
Hospital discharge					X	X	X	X	X	X

Visit	V1	V2		V3		V4	V5	V6	V7	V8
Assessment of COVID complications [22]		X	X	X	X	X	X	X	X	X
Prior/concomitant medication[23]	X	X	X	X	X	X	X	X	X	X
AE		X	X	X	X	X	X	X	X	X
Blood samples for PK, only for participating in the sub-study[24]		X	X	X	X		X			

1 At the time of the diagnosis of infection by COVID-19
2 Description of the drug, dose.. Medication must be prepared by designated unblinded staff.; it will be administered in 100 ml i.v. infusion over 50 min. During the infusion, the medical staff in charge will be present for safety evaluation.
3 On day 4, discharge from the hospital could be granted if the patient is clinically stable
4 Medical history/history of underlying diseases includes referenced by the patient:
o Cardiovascular disease: coronary artery disease/ischemic cardiomyopathy documented by non-invasive studies such as ergometry, ECHO, nuclear magnetic resonance (i.e. alterations in myocardial perfusion), single photon emission computer tomography (SPECT) and positron emission tomography (PET) showing ischemic myocardium. History of revascularisation surgery, stenting, acute myocardial infarction, or angina. By invasive methods such as angiography. High blodd pressure defined as a record of SBP > 140 mmHg, DBP > 90 mmHg, or both, or SBP > 135 mmHg, DBP > 85 mmHg in the 24-hour outpatient blood pressure monitoring.

- o Chronic obstructive pulmonary disease/asthma: defined in spirometry as obstruction with some degree of reversibility in spirometric test but the FEV1/FVC ratio will never completely normalize in the case of COPD and as a history of diagnosis of Asthma with or without abnormal spirometry. History of tuberculosis.
- o Kidney disease according to the glomerular filtration rate (< 90 ml/min/1.73 m2 is considered renal damage) calculated by the Cockcroft-Gault formula; GFR, glomerular filtration rate estimated by the abbreviated formula of the MDRD study (Modification of Diet in Renal Disease).
- o Blood glucose > 200 mg/dl at any time of the day or fasting > 126 mg/dl (7 mmol/l) or more in two individual A1C tests of 6.5% or more in two individual tests.
- o Liver disease alteration in the laboratory parameters of the hepatogram and/or compatible images History of transplantation-related treatment with immunosuppressants/immunomodulators, HIV infection.
- o Neurological disability or any neurological disease that affects the strength of the rib cage such as amyotrophic lateral sclerosis, neuromuscular (Eaton-Lambert, myasthenia), myopathies (dystrophies, metabolic, polymyositis/dermatomyositis, congenital and progressive) Guillain-Barré. Other clinically relevant diseases.

5 The SARS-CoV-2 PCR test result must be positive before the IA/CF can be obtained for the study. The source document with this result must be attached to the patient's medical record.

6 Confirm eligibility criteria before administration of study drug

7 Physical exam: height in cm (may be referred); body weight in kilograms; general appearance; skin and mucous; membranes; head, ears, eyes, nose, throat; neck; adenopathies; respiratory system; cardiovascular system; abdomen; musculoskeletal system; central nervous and peripheral system; other

The BMI (height (cm)/weight $(kg)^2$) must be calculated. The weight measurement that was made in the initial screening assessment will be used for the calculation of the dose.

8. Vital signs measurements (i.e. SBP, body temperature, pulse, and respiratory rate) are recommended after the subject has been in the supine position for at least 3 min.
9. 24 h +/- 2 h after the end of study drug administration
10. They must be obtained immediately prior to study drug administration (approximately within 15 min) and within 15 min after completion of study drug administration.
11. **Haematology:** platelet count, erythrocyte count, haemoglobin, haematocrit, white blood cell count, neutrophils, lymphocytes, eosinophils (relative formula).

12. Laboratory results must be obtained within 24 h of the 1st. administration of study drug. Results should be available and reviewed prior to randomisation. If there is any change in clinical presentation within 24 h of the 1st. administration of study drug, laboratory evaluations should be repeated, and the results of such tests should be reviewed prior to administration of study drug. The results will be acceptable if they were obtained within the last 24 h of V2, as long as they were carried out in the local laboratory of the institution participating in the clinical trial.
13. **Serum biochemistry tests** will include the following: urea, creatinine, glycaemia, potassium, sodium, AST/ALT, alkaline phosphatase, total and direct bilirubin, total protein, albumin, LDH DH
14. In women of childbearing age (urine or blood according to the usual practice of the site)
15. 8-point WHO scale: 0 = no evidence of infection, 1 = outpatient, with no activities limitation; 2 = outpatient, with activities limitation; 3 = hospitalised with no oxygen therapy required; 4 = oxygen therapy employing a mask; 5 = non-invasive ventilation or high flow oxygen; 6 = Mechanical ventilation; 7 = mechanical ventilation and organ support (vasopressors, ECMO, RRT); 8 = Death
16. It should be done by the unblinded study staff through a randomisation sealed envelope system. The first 12 subjects will be randomised through a centralised system. An appropriate instruction manual will be provided to the site.
17. Should only be carried out in V2 if > 24 h have elapsed since the initial screening assessment
18. COVID-19 history and symptoms assessment:
    - Symptoms according to the definition of case by the Ministry of Health of Argentina: fever (37.5 °C or more), cough, odynophagia, shortness of breath, new onset anosmia/dysgeusia, others (nausea, vomiting, abdominal pain, diarrhoea, asthenia, headache, myalgia, nasal congestion, others). The start date, severity and follow-up must be verified to evaluate resolution/worsening during the 28 days that the study lasts.
    - History of the disease: date of first symptom
    - Category of the disease according to NIH classification: mild, moderate, severe, critical.

19. Blood samples immediately prior to 1st. administration of study drug, on day 7 and on day 21 for viral load detection. These samples will be sent to a central laboratory. More information will be provided in the study laboratory manual.
20. Blood sample immediately before 1st. administration of the study drug, on day 7 and on day 21 for biomarkers (troponin T, D-dimer, ferritin, and C-reactive protein), anti-SARS-CoV-2 antibodies, immunogenicity test and future analysis. These samples will be sent to a central laboratory. More information will be provided in the study laboratory manual.

21 To be obtained within approximately 15 min after completion of each study drug administration and prior to hospital discharge (V3-Day 4).

Injection site reaction (definition: a disorder characterised by a severe adverse reaction - usually immune - at the site where an injection is given). Classified by CTCAE criteria

1 = Pain at palpation with or without associated symptoms (e.g. warmth, erythema, itching).
2 = Pain; lipodystrophy; oedema; phlebitis.
3 = Ulceration or necrosis; severe tissue damage; surgical intervention indicated.
4 = Life threatening consequences; emergency intervention indicated.
5 = Death

Hypersensitivity reactions

To be obtained within approximately 15 min after completion of each study drug administration and prior to hospital discharge (V5) and at each subsequent visit until V8.

Allergic reaction: (definition: disorder characterised by local or generalised adverse response to exposure to an allergen):

1 = Transient symptoms of hot flashes or rash, drug fever < 38 °C; intervention not indicated.
2 = Intervention or interruption of the indicated infusion; responds quickly to symptomatic treatment (e.g. antihistamines, nonsteroidal anti-inflammatory drugs, narcotics).
3= Prolonged (e.g. does not respond rapidly to symptomatic medication and/ or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalisation indicated for clinical sequelae (e.g. renal impairment, pulmonary infiltrates).
4 = Life threatening consequences; emergency intervention indicated.
5 = Death

Anaphylaxis:(definition: a disorder characterised by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, generating a hypersensitivity immune response; clinically, it presents with shortness of breath, dizziness, hypotension, cyanosis, and loss of consciousness, and can lead to death). Categorised by CTCAE criteria:

1 = Not applicable
2 = Not applicable
3 = Symptomatic bronchospasm, with or without urticaria, parenteral intervention indicated; oedema/angioedema of allergic origin; hypotension
4 = Life threatening consequences; emergency intervention indicated.
5 = Death

Serum sickness disease: (definition: a disorder characterised by a delayed hypersensitivity reaction to foreign proteins derived from animal serum. It occurs approximately 6 to 21 days after administration of the foreign antigen. Symptoms include fever, arthralgia, myalgia, rashes, lymphadenopathy, marked chest discomfort, and dyspnoea). Categorised by CTCAE criteria:

1 = Asymptomatic; clinical or diagnostic observations only; intervention not indicated.
2 = Moderate arthralgia; fever, rash, hives; indicated antihistamines
3 = Arthritis or severe arthralgia; generalised rash; steroids or i.v. fluids indicated.
4 = Life threatening consequences; vasopressors or mechanical ventilation support indicated.
5 = Death

22. Assessment of MV requirement, transfer to ICU and death.
23 **Concomitant medication** description, dose, dosage and start date within the last 7 days of V1.
24 Blood sample for PK assessments from subjects participating in the PK sub-study immediately before the 1st. administration of the study drug, at the end of the 1st. administration of the study drug, 24 h after the 1st. administration of the study drug, immediately before the 2nd. administration of the study drug, at the end of the 2nd. administration of the study drug, 24 h after 2nd. study drug administration, and 7 days after 1st. study drug administration. The PK study will be carried out only in pre-selected institutions and a separate consent will be provided.
25. As from Day 5, if the patient is under outpatient follow-up, Visits on day 5, 7, 14, and 28 will be on the telephone. In those cases, invasive procedures will not be performed.
26 The imaging taken as part of the evaluation of the the patient's institution SoC, will be accepted for confirmation of pneumonia, despite the fact that it is prior to Day 0.

5 POPULATION

5.1 Target population

Patients with moderate or severe COVID-19 as defined by NIH (74), which requires hospitalisation, excluding patients with assisted ventilation or admission in the ICU.

5.2 Number of subjects

The recruitment of 242 patients in approximately 10 sites is planned. After approximately 145 subjects complete their follow-up (60% of the original sample), an interim analysis will be carried out to define whether it is necessary to adjust the sample size to the event rate; an increase of up to 72 individuals will be allowed (n = 314).

5.3 Inclusion and Exclusion criteria

Subjects must meet all the inclusion criteria at Screening:

1. Patients of both sexes aged 18 to 79 years of age

2. SARS-CoV-2 infection confirmed by PCR

3. Patients with moderate or severe disease by NIH definition, requiring hospitalisation.

4. Acceptance to participate in the study by the signature of the informed consent by a subject or their relative, if applicable

5. Be within 10 days of the onset of symptoms at the time of the Screening visit according to a case definition from the National Ministry of Health

6. Female patients of child-bearing age with negative pregnancy test

Subjects must not meet any of the following exclusion criteria at the time of screening

1. Patients who have received treatment with plasma from COVID-19 convalescents

2. Patients who are participating in other therapeutic clinical trials

3. Patients who require mechanical ventilation or who are hospitalised in the ICU at the screening visit

4. History of anaphylaxis, prior administration of equine serum (e.g. anti-tetanus serum or anti-ophidic serum or anti-arachnid toxin serum) or allergic reaction due to contact or exposure to horses

Note: the production of anti-tetanus serum of equine origin stopped in 1970, and therefore a patient who used it after that date could be a candidate for the study since the serum is of human origin.

5. Pregnant or breastfeeding women

6. Patients who, at the doctor's judgement, are likely to die within the next 30 days due to a concomitant disease other than the study disease

7. Patients who are expected to be referred to another institution within 72 hours of recruitment, which prevents adequate follow-up of that patient

5.4 Patient selection

The subject or the subject's legal guardian, if applicable, must sign an AF/CF before any of the procedures related to the study can be carried out.

5.5 Deviations from the Inclusion and Exclusion criteria

No deviation from what is established in the inclusion and exclusion criteria will be allowed. The investigator may contact the Medical Monitor to discuss the eligibility of a particular subject.

6 CONDUCT OF THE STUDY

6.1 Study procedures

Those patients who are hospitalised with a diagnosis of moderate to severe COVID in the participating centres will have the study explained and informed consent will be provided. Once the consent process is concluded, if the patient agrees and signs the IA/CF, they will undergo a screening process to ensure their eligibility for the study.

6.2 Study procedures by time-point

6.2.1 Visit 1 - Screening

The subject or the subject's legal guardian and/or, if applicable, must provide their assent/consent so that the subject can undergo the screening process necessary for participation in the study, through the signature of an IA/CF.

The screening visit (V1) must take place within 10 days of the onset of coronavirus symptoms after obtaining the result of the diagnostic tests for SARS COV 2. After the confirmation of positive results in the test by PCR, performed according to the site’s SoC, the study staff will perform the following:

- **Informed consent process and signature of the informed consent.**

The particular situation related to the extreme transmission and virulence of COVID-19, raises new challenges related to the documentation of the informed consent process (75-76). In that order, when the usual mechanisms are not possible, it is necessary to consider alternative forms. For example, contacting patients by video calls, developing a record of consents by audiovisual means or digital images, obtaining oral consents supplemented with confirmation by email and entry in the Medical Record with the signature of one or more health professionals.

Taking into account that the “paper” consent signed by the patient is a source of potential transmission of COVID-19, an alternative signature process is proposed:

The investigator signs and dates 2 copies of the consent, after the process described above has occurred, and before entering the patient's room. Then, if the patient agrees to participate, they will be asked to sign and date the same document. The patient will be asked to obtain a photo of the signature page and send it to the investigation team in order to have a safeguard

that the process was carried out. The patient retains one of the forms and the other CF will be protected in a transparent plastic sheet, which when leaving the room will be placed in a secondary envelope for a period of 72 hours. After this time, it is removed from the secondary envelope, the plastic sheet is cleaned with alcohol and the copy is filed in the regulatory folder of the study or in the patient's medical record.

- **Demographics:**

Age: in years

Sex: male/female

Ethnicity: White, Blanc, mixed Asian, Indigenous or other

- **Clinical history:**

Relevant medical history (description and date of diagnosis)

History of comorbidities:

- Cardiovascular disease
- Any chronic pulmonary disease
- Kidney disease
- Diabetes
- Liver disease
- Immunocompromised
- Neurological disability
- Others

Allergies to medications and/or horses

Concomitant medication description, dose, dosage and start date within the last 7 days.

Any medical condition that after signing the informed consent should be informed as an adverse event (AE).

- History of the disease:
  - Date of the first symptom

- Symptoms according to the definition of case by the Ministry of Health of Argentina (77): Fever (37.5°C or higher), Cough, Odynophagia, Shortness of breath, New-onset anosmia/dysgeusia, others

- Patient classification according to the 8-point WHO scale (78)

  0- No evidence of infection

  1- Outpatient, with no limitation to activities

  2- Outpatient, with limitation to activities

  3- Hospitalised with no oxygen needed

  4- Use of oxygen with mask

  5- Non-invasive ventilation or high-flow oxygen

  6- Mechanical ventilation

  7- Mechanical ventilation and organ support (vasopressors, ECMO, RRT)

  8- Death

- Vital signs

  • Heart rate

  • Respiratory rate

  • Oxygen saturation: obtained from the measurement of arterial gases or using the pulse oximeter. In addition, the inspired fraction of oxygen the patient receives will be documented as follows:

  - Ambient air FiO2: 0.21
  - Nasal tube to FiO2 0.24 (1 l/min); 0.28 (2 l/min); 0.32 (3 l/min) or 0.36 (4 l/min)
  - Face mask with nasal tube: 0.24 (3 l/min); 0.28 (4 l/min); 0.31 (6 l/min); 0.35 (8 l/min); 0.4 (10 l/min); 0.45 (12 l/min), and 0.5 (15 l/min)
  - Mask with reservoir 0.9-1 (10-15 l/min)

  • Supine blood pressure

• Temperature

- Full physical exam:

  Height in cm, body weight in kilograms, BMI

  General appearance

  Skin and mucous membranes

  Head, Ears, Eyes, Nose, Throat

  Neck

  Adenopathies

  Respiratory system

  Cardiovascular system

  Abdomen

  Musculoskeletal system

  Central nervous and peripheral system

  Other

- **Laboratory tests**

- Haematology Platelet count, erythrocyte count, haemoglobin, haematocrit, neutrophils, lymphocytes, eosinophils.

- Full chemical panel Urea, Creatinine, Glycaemia, Potassium, Sodium, AST/ALT, Alkaline Phosphatase, Total and Direct Bilirubin, Total Protein, Albumin, LDH.

- Pregnancy test, if applicable.

- **12-lead ECG**
- **Imaging**

- Chest X-ray; description of the type of infiltrate, affected areas and/or

- Chest TC; description of the type of infiltrate, affected areas.

- **Eligibility criteria**

- Inclusion criteria confirm all inclusion criteria are met

- Exclusion criteria confirm that no exclusion criteria are met

Note on laboratory samples: laboratory results prior to V1 will be accepted if they have been obtained during the admission of the patient evaluated for COVID-19 according to SoC of each institution. The results will be acceptable if they were obtained within the last 24 h of V1, as long as they have been performed in the local laboratory of the institution participating in the clinical trial.

The administration of the study drug should be done as soon as possible after obtaining the results of the Screening visit (V1)

6.2.2 Visit 2. Baseline

6.2.2.1Day 1 - First dose of treatment

Must be done within 24 h of the screening visit**.**

- Physical exam and laboratory tests if more than 24 h have elapsed.
- Assessment of COVID symptoms if more than 24 h have elapsed.
- Patient classification according to the WHO scale if more than 24 h have elapsed.
- Confirm eligibility
- Randomisation to treatment assignment by unblinded staff

Prior to the start of administration of study drug:

- Notify the pharmacy to prepare the study drug for its administration.
- Preparation of the infusion by the unblinded staff
- Prepare the subject for i.v. infusion per standard operating procedure.
- Vital signs 15 min prior to infusion
- For PK sub-study: pre-infusion blood sample for the pharmacokinetics
- Samples for viral load
- Blood samples for anti-SARS-CoV-2 antibodies, biomarkers and immunogenicity

- Administration of double-blind treatment: i.v. infusion of 100 ml over 50 min per standard operating procedures (Section 8.3)

Post-treatment administration procedure:

- For PK sub-study: Study samples for pharmacokinetics (5 min after the end of infusion)
- Vital signs within 15 min post-infusion.
- Assessment of hypersensitivity reactions within 15 min post-infusion.
- Assessment of adverse events (Sections 9 and 10) and concomitant medication

6.2.2.2 Day 2 - 1st. dose follow-up

- Assessment of COVID-19 disease and complications
- Safety laboratory 24 h post-infusion

Haematology Platelet count, erythrocyte count, haemoglobin, haematocrit, neutrophils, lymphocytes, eosinophils.

Full chemical panel Urea, Creatinine, Glycaemia, Potassium, Sodium, AST/ALT, Alkaline Phosphatase, Total and Direct Bilirubin, Total Protein, Albumin, LDH.

- Vital signs
- Patient classification according to the WHO scale
- Assessment of hypersensitivity reactions
- Assessment of adverse events and concomitant medication

6.2.3 Visit 3

6.2.3.1 Day 3 Second dose of treatment

- Assessment of COVID-19 disease and complications
- Assessment of adverse events (Sections 9 and 10) and concomitant medication
- Patient classification according to the WHO scale
- Assessment of adverse events and concomitant medication
- Assessment of hypersensitivity reactions

Prior to the start of administration of study drug:

- Preparation of the infusion by the unblinded staff

- Vital signs within 15 min prior to the infusion (SBP, body temperature, pulse and respiratory rate).
- For PK sub-study: pre-infusion blood sample for the pharmacokinetics

- Administration of double-blind treatment: 100 ml infusion over 50 min

Post-treatment administration procedure:

- For PK sub-study: Study samples for pharmacokinetics (5 min after the end of infusion)
- Vital signs within 15 min post-infusion.
- Assessment of hypersensitivity reactions within 15 min post-infusion
- Assessment of adverse events and concomitant medication

6.2.3.2 Day 4 2nd dose follow-up

- Assessment of COVID-19 disease and complications
- For PK sub-study: Study samples for pharmacokinetics (24 h post second infusion)

- Safety laboratory 24 h post-infusion

Haematology Platelet count, erythrocyte count, haemoglobin, haematocrit, neutrophils, lymphocytes, eosinophils.

Full chemical panel Urea, Creatinine, Glycaemia, Potassium, Sodium, AST/ALT, Alkaline Phosphatase, Total and Direct Bilirubin, Total Protein, LDH.

- Vital signs
- Patient classification according to the WHO scale
- Assessment of hypersensitivity reactions
- Assessment of adverse events (Sections 9 and 10) and concomitant medication

The subject will be **discharged** if he/she is clinically stable and per medical judgement.

6.2.4 Visit 4- Day 5 follow-up

- Vital signs (SBP, body temperature, pulse and respiratory rate).

- Patient classification according to the WHO scale
- Assessment of COVID-19 disease and complications
- Assessment of hypersensitivity reactions
- Assessment of adverse events (Sections 9 and 10) and concomitant medication

6.2.5 Visit 5- Day 7 follow-up

- Vital signs (SBP, body temperature, pulse and respiratory rate).
- Patient classification according to the WHO scale
- Assessment of COVID-19 disease and complications
- Assessment of hypersensitivity reactions (Section 7.2.5)
- Assessment of adverse events (Sections 9 and 10) and concomitant medication
- Samples for viral load
- Blood samples for anti-SARS-CoV-2 antibodies and biomarkers
- For PK sub-study only: pre-infusion blood sample for the pharmacokinetics

Schedule a visit to the clinic to be conducted on Day 14.

6.2.6 Visit 6 - Day 14 follow-up

The subject should be examined in the clinic 14 days (± 1 day) after the 1st. administration of the study drug. This visit may be carried out at the subject's home, if necessary. At this visit, the study staff undertake the following:

- Vital signs (SBP, body temperature, pulse and respiratory rate).
- Patient classification according to the WHO scale
- Assessment of COVID-19 disease and complications
- Assessment of hypersensitivity reactions (Section 7.2.5)
- Assessment of adverse events (Sections 9 and 10) and concomitant medication

Schedule a visit to the clinic to be conducted at Week 3 (± 2 days) after the 1st. administration of the study drug.

6.2.7 Visit 7 - Day 21 follow-up

- Vital signs (SBP, body temperature, pulse and respiratory rate).

- Patient classification according to the WHO scale
- Assessment of COVID-19 disease and complications
- Assessment of hypersensitivity reactions (Section 7.2.5)
- Assessment of adverse events (Sections 9 and 10) and concomitant medication
- Samples for viral load
- Blood samples for anti-SARS-CoV-2 antibodies, immunogenicity and laboratory markers
- Safety laboratory tests:

    a. Haematology

    b. Serum chemistry

6.2.8 Visit 8- Day 28 - End of study

The subject should be examined in the clinic 28 days (± 2 days) after the 1st. administration of the study drug. This visit should also be carried out if the subject prematurely discontinues participation in the study. This visit is considered the End of Study (EOS) visit for all subjects.

- Vital signs (SBP, body temperature, pulse and respiratory rate)
- Patient classification according to the WHO scale
- Assessment of COVID-19 disease and complications
- Assessment of hypersensitivity reactions (Section 7.2.5)
- Assessment of adverse events (Sections 9 and 10) and concomitant medication

6.3 Early termination

If the subject's participation in the study is prematurely interrupted for any reason, the reason for such Early Termination (ET) must be documented, and the V8 (EOS) procedures must be performed as indicated in Section 6.2.8.

The electronic CRF (eCRF) Case Report Form Termination page must be completed for each subject to whom the study drug has been administered, regardless of whether the subject has completed the study or not. In this form the reason for the ET must be indicated; as much information as possible should be provided. The primary reason for the early termination of the subject’s participation should be selected from the following standard ET categories:

- *Adverse event:* There have been clinical or laboratory events that, based on the investigator's medical judgment, make the termination of the subject's participation to be

in the best interest of the subject. This includes serious and non-serious AEs, regardless of their relationship to IMP.

- *Death:* The subject died.
- *Withdrawal of consent:* The subjects or their caregivers decided not to continue participating in the study, without there being a medical need determined by the investigator for such withdrawal. If the subject stated the reason for the withdrawal, such reason must be recorded in the CRF.
- *Failure to meet the randomisation requirements:* Subject does not meet eligibility criteria during reassessment at Visit 2 (Dose 1), prior to randomisation.
- *Protocol violation:* The findings or the subject's behaviour did not meet the criteria for entry to the protocol or did not meet the requirements of the protocol (e.g. non-compliance with the drug regimen, non-compliance with the stipulated number of visits). This violation required premature discontinuation of participation in the study.
- *Lost to follow-up:* Subject stopped attending visits and could not be contacted by study staff.
- *Non-compliance:* Subject did not comply with study visits or procedures.
- *Others:* Study participation was interrupted for any reason that is not amongst the aforementioned, such as the case that the study is definitively interrupted by INMUNOVA or at the discretion of the investigator.

7 DESCRIPTION OF THE STUDY PROCEDURES

7.1 Efficacy evaluations

The investigator will document whether the subject has an improvement within 28 days of the administration of the first dose. A responder subject is defined as a subject with an improvement in at least 2 categories in the 8-point WHO clinical status ordinal scale or hospital discharge.

Patient classification according to the WHO scale (78)

0- No evidence of infection

1- Outpatient, with no limitation to activities

2- Outpatient, with limitation to activities

3- Hospitalised with no oxygen needed

4- Use of oxygen with mask or nasal tube

5- Non-invasive ventilation or high-flow oxygen

6- Mechanical ventilation

7- Mechanical ventilation and organ support (vasopressors, ECMO, RRT)

8- Death

7.2 Safety evaluations

7.2.1 Electrocardiogram

12-lead ECGs will be performed on hospital/clinic electrocardiographs at Screening (V1). ECG results will be documented in eCRF.

7.2.2 Vital signs

Vital signs to be measured are: SBP, body temperature, pulse and respiratory rate. Vital signs will be obtained at Screening (V1), immediately prior to study drug administration (within 15 min), within 15 min after study drug administration is completed, and at follow-up visits.

7.2.3 Clinical laboratory analysis

Blood samples will be obtained in Screening (V1), V2, V3 and V7, and in other visits if the clinical presentation of the subject warrants it, for the following:

- *Haematology:* Hb, Hct, RBC count, WBC count (with differential con [lymphocytes, neutrophils, eosinophils]) and platelet count.

- *Biochemistry:* alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin, urea, creatinine, alkaline phosphatase (ALP), LDH, Na, potassium, albumin, and glucose.

Laboratory samples will be analysed in the local/hospital laboratory. Normal laboratory ranges will be collected from each laboratory used to process the samples. The investigator should read the clinical laboratory results in a timely manner to assess the clinical significance of any abnormalities that may be present. In the event of an unexplained clinically significant abnormal laboratory value, the test in question should be repeated and followed until the parameter has returned to the normal range and/or an adequate explanation for the abnormality has been found.

7.2.4 Adverse events

All AE that occur within the period from the moment the subject or the subject's guardian signs the AF/CF until the last study procedure is carried out will be recorded. All AEs that occurred prior to the start of the study drug administration session (i.e., prior to administration of study drug in V2) will be recorded as medical history. All AE that are in progress at the time of V8 (EOS/ET) will be followed up until their resolution or until they are no longer clinically significant at the discretion of the investigator.

See Sections 9 and 10 to for additional information.

7.2.5 Adverse event of special interest

The Common Terminology Criteria for Adverse Events (CTCAE) will be used to assess injection site reactions and hypersensitivity reactions during the study. These will be assessed any time they occur during the course of the study, but specifically within 15 min after each administration of the study drug is completed.

7.2.5.1 Injection site reaction

A disorder characterised by a severe adverse reaction (usually immune) that occurs at the site where an injection is given. Categorised by CTCAE criteria:

1 = Pain on palpation with or without associated symptoms (e.g. warmth, erythema, itching).

2 = Pain; lipodystrophy; oedema; phlebitis.

3 = Ulceration or necrosis; severe tissue damage; surgical intervention indicated.

4 = Life threatening consequences; emergency intervention indicated.

5 = Death

7.2.5.2 Hypersensitivity reaction

A hypersensitivity reaction comprises various levels of allergic reaction, both acute and delayed. Allergic reaction events, anaphylaxis, and serum sickness will all be evaluated using CTCAE criteria. The management of anaphylactic reactions should be carried out following the guidelines established in Appendix 2.

7.2.5.2.1 Allergic reaction

An allergic reaction is disorder characterised by a local or generalised adverse response to exposure to an allergen. Categorised by CTCAE criteria:

1 = Transient symptoms of hot flashes or rash, drug fever < 38 °C; intervention not indicated.

2 = Intervention or interruption of the indicated infusion; responds quickly to symptomatic treatment (e.g. antihistamines, nonsteroidal anti-inflammatory drugs, narcotics).

3= Prolonged (e.g. does not respond rapidly to symptomatic medication and/ or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalisation indicated for clinical sequelae (e.g. renal impairment, pulmonary infiltrates).

4 = Life threatening consequences; emergency intervention indicated.

5 = Death

7.2.5.2.2 Anaphylaxis:

Anaphylaxis is a disorder characterised by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, which generates a hypersensitive immune response. Clinically, it presents with shortness of breath, dizziness, hypotension, cyanosis, and loss of consciousness, and can lead to death. Categorised by CTCAE criteria:

1 = Not applicable

2 = Not applicable

3 = Symptomatic bronchospasm, with or without urticaria, parenteral intervention indicated; oedema/angioedema of allergic origin; hypotension

4 = Life threatening consequences; emergency intervention indicated.

5 = Death

7.2.5.2.3 Serum sickness:

Serum sickness is a disorder characterised by a delayed hypersensitivity reaction to foreign proteins derived from animal serum. It occurs approximately 6 to 21 days after administration of the foreign antigen. Symptoms include fever, arthralgia, myalgia, rash, lymphadenopathy, marked chest discomfort, and dyspnoea. Categorised by CTCAE criteria:

1 = Asymptomatic; clinical or diagnostic observations only; intervention not indicated.

2 = Moderate arthralgia; fever, rash, hives; indicated antihistamines

3 = Arthritis or severe arthralgia; generalised rash; steroids or i.v. fluids indicated.

4 = Life threatening consequences; vasopressors or mechanical ventilation support indicated.

5 = Death

7.3 Other assessments

7.3.1 General survival

Assessment of survival (i.e., the number of days elapsed between 1st. administration of the study drug until death, if applicable) in all visits

7.3.2 Complications of COVID infection

The investigator will document if the subject requires: ICU admission, MRA, or dies, classifying it as absent/present until day 28.

7.3.3 Other secondary endpoints:

Pharmacokinetic parameters of INM005

Evolution of the disease

Time to response to treatment

Viral load levels of SARS CoV-2

7.3.4 Exploratory endpoints

Anti-SARS-CoV 2 antibodies levels

Measurement of Troponin T, D-dimer, ferritin, LDH, C-reactive protein at baseline, days 7 and 21.

Level of anti INM005 antibodies

7.3.4.1.1 Duration of hospitalisation

The length of stay in the hospital institution will be calculated taking into consideration the period between the date of admission and the date of hospital discharge for all subjects, taking into account that a minimum of 4 days of hospitalisation is required for all subjects enrolled given the drug administration schedule established by the protocol.

7.3.4.1.2 Mortality predictors

The following predictors of mortality will be evaluated at the time of hospital admission:

Age

Comorbidities: diabetes, chronic obstructive disease, high blood pressure and coronary disease

Respiratory Rate > 24 breaths/min

SOFA score

White blood cell count

Lymphocyte count

AST level > 40 U/l

Creatinine

LDH

CPK

D-dimer

Prothrombin time

Serum ferritin

IL-6

7.4 Sample for immunogenicity testing and future analysis

7.4.1 Immunogenicity assessments

Screening tests for antidrug antibodies (ADAs) are of fundamentally important in determining safety when biologics are being used. Immunogenic responses can lead to anaphylaxis, cytokine release syndrome, cross-reactivity to endogenous proteins, or neutralising antibodies that can affect the efficacy of the therapeutic product. Regulatory guidelines state that a method for the detection of drug-specific antibodies must be developed, as well as a method for determining whether any of the anti-drug antibodies are neutralising antibodies or are simply binding antibodies. In addition, clear thresholds should be established for "positive" and "negative" screening test results for ADAs. The frequency of testing for ADAs may be determined in part by non-clinical results (79).

Specific patient attributes can also influence immunogenicity. Such attributes may be the patient's immune status, prior sensitisation to the product under study, and the dose, route, and frequency of administration. As noted in the aforementioned guidelines, the intradermal, subcutaneous, and inhalable routes of administration are associated with increased immunogenicity compared to the intramuscular and intravenous routes, with the intravenous route generally being considered the least immunogenic. Increased product administration such as that of the multiple dose paradigm can lead to Ig class change and increased affinity antibody responses. Since the maximum number of administrations of INM005 in the proposed study is limited to 2 i.v. administrations by within a 48-hour period, the probability of higher magnitude affinity responses is considered nil.

7.4.2 Biological properties of INM005

INM005 is an antibody fragment of equine origin, and as such has the ability to induce an immune response. To reduce its potential immunogenic properties, the Fc region has been removed. This feature, combined with the fact that INM005 is administered intravenously as a single dose (or as two doses), it further reduces its potential to cause unwanted immune reactions. However, there is a variable incidence of type III hypersensitivity reactions (serum sickness) amongst products that are similar to this one, which are triggered by the formation of immune complexes in which ADAs participate (Section 1.3), which will be evaluated in this clinical study.

Finally, a method has been developed to detect drug-specific antibodies, and thresholds have been established for the categories of “positive” and “negative” results of the ADA detection tests during the development of the Phase I study. The frequency determined for ADA testing is before the administration and 28 days after administration.

7.4.3 Immunogenicity reactions - Phase I

No AE compatible with immunogenicity reactions were observed in a phase 1 study in healthy adult volunteers that has already been completed with INM004. An immunogenicity assessment for the product INM004 was carried out with the samples from the 11 subjects enrolled in Stage I and Stage II (Section 1.3.4). It was concluded that, for serum samples obtained 30 days after administration, there was no change in reactivity to the immobilised product. There were no clinical observations that could indicate the presence of immunogenicity reactions, and no antidrug antibodies were detected in any of the samples tested.

With the understanding that the clinical assessment will ultimately determine the diagnosis of hypersensitivity reactions, the study of the formation of antibodies as a consequence of the administration of the product will be based on the immunomolecular evaluation.

7.4.4 Sample for immunogenicity testing and future analysis

Blood/serum samples will be extracted for future analysis. Future analyses include evaluations of biomarkers related to COVID-19 disease or potential drug-induced side effects; these tests will under no circumstances include genetic testing. These analyses will contribute to establishing the safety and efficacy profile of INM005. The samples will be kept frozen at -20°C for a period of 5 years; once this period is over, they will be destroyed. All samples will be processed and transported as indicated in the Study Manual. The sponsor may send the samples to 1 or more laboratories for analysis, according to what is indicated in the Study Manual. Analyses made from these samples could lead to scientific publications. The data will be analysed in the context of this study, but may also be explored in combination with data from other studies. Access to these samples will be restricted to authorised staff, and the privacy and confidentiality of the subject will be preserved at all times, since all data will be anonymised for exploratory analysis.

Blood/serum samples will also be obtained for immunogenicity tests as indicated in the previous paragraphs. The samples will be processed and transported as indicated in the Study Manual. The sponsor may send the samples to 1 or more laboratories for analysis, according to what is indicated in the Study Manual.

7.5 Pharmacokinetics

A blood sample will be drawn from subjects in the PK sub-study (20 subjects) for PK tests immediately before the 1st. administration of the study drug, at the end of the 1st. administration of the study drug, 24 h after the 1st. administration of the study drug, immediately before the 2nd administration of the study drug, at the end of the 2nd administration of the study drug, 24h after 2nd study drug administration and 7 days after 1st. study drug administration.

7.6 Protocol deviations

All deviations from what is established by the protocol will be evaluated and documented individually for each case prior to closing the database, and those that, as considered, have

serious repercussions on the efficacy results will lead to the subject in question is excluded from the analysis. Major protocol deviations will be fully characterised in the SAP.

Deviations from the protocol will be summarised by centre and grouped into different categories. The major deviations described below will result in the exclusion of the subject from the PP population, as indicated in section 11.2:

- Subjects who entered the study despite not meeting the entry criteria.
- Subjects who developed any of the criteria for withdrawal during the study, but were not withdrawn.
- Subject who received 1 (or none) of the 2 doses established in the protocol
- Subjects who received the wrong treatment or the wrong dose.
- Subjects who received compassionate treatment with convalescent serum or antivirals or immunomodulators without having developed the primary event.
- Subjects who, without having developed the primary event, did not complete the 28-day follow-up.

8 MANAGEMENT OF THE STUDY DRUG

8.1 Description

8.1.1 Dosage Form

The dosage form is described in Table 8.1.

Table 8.1 Data of the investigational medicinal products

Active pharmaceutical ingredient:	anti-SARS-CoV-2 F(ab’)2 fragments of equine immunoglobulins
Concentration:	Each ml of the medicinal product contains purified equine immunoglobulins (F(ab')2 fragments) with the capacity to neutralise the cytopathic effect of the SARS-CoV-2 exerted in vitro on the Vero cell line, in at least a 1:2000 dilution. Each ml contains 30 mg of protein (equine immunoglobulins, F(ab')2 fragments). The product contains phenol in amounts less than 2.5 mg/ml, which is used as a preservative during the manufacturing process.
Presentation:	INM005 is presented as a sterile solution for intravenous administration (5 ml vial).

8.1.2 Storage conditions

Refrigerated storage at 2-8°C (range 1.5 to 8.4°C) Under these conditions, INM005 can be stored for up to 36 months from the date of manufacture (stability studies are underway to confirm shelf life). Do not freeze. Once the vial has been perforated, the contents should be used to prepare the infusion bag and should be administered as soon as possible within a maximum period of 4 h. INM005 vials are intended for single use only and contain no preservatives. Any remainder must be discarded.

In the event that a deviation in temperature occurs during storage, the investigator must contact the sponsor within 24 h of becoming aware of the deviation through the specific study form. The Sponsor will inform the investigator in writing whether the vials are suitable for use or not. The procedure is described in detail in the Study manual.

The investigator is responsible for taking all the necessary measures to keep adequate records and ensure the supply, handling, storage, distribution and use of these materials, in accordance with the protocol and the regulations and laws in force on the matter.

8.2 Conditioning and transport

INM005 is presented in 10 ml glass vials, with a butyl rubber stopper and an aluminium seal, with a flip-top plastic cap, with a fill volume of 5 ml per vial. Each vial is packed in an individual cardboard box.

8.3 Dosage and administration

For i.v. use only. The dose of the IMP must be administered as shown in Table 8.2.

Table 8.2 Data related to the administration of the investigational medicinal product

Patient group	Dose	Rate of the infusion	Duration of the infusion	Volume of infusion
Adult patients	4 mg/kg of body weight	2.0 ml/min	50 min	100 ml

Abbreviations: kg, kilograms; mg, milligrams; min, minutes; ml, millilitres

Preparation of the dose for the active treatment/placebo arm:

The dose of the IMP is 4 mg of protein/kg of subject body weight. Each vial contains 30 mg of protein/ml. Therefore, each subject should receive 0.13 ml/kg.

The IMP should be prepared as follows. According to the subject's body weight, the number of vials required to prepare the indicated dose should be calculated according to the following formula:

V (ml/subject) = (P × 0.13 ml/kg), in which P is the body weight expressed in kg.

The calculated IMP volume will be added to the 100 ml physiological saline infusion bag. Two doses of IMP will be administered as an infusion at a rate of 2.0 ml/min over a 50-minute period with a 48-hour interval between doses.

8.4 Accountability

The investigator must keep an accurate accounting of the quantity of IMP units delivered to the centre, administered to subjects, and returned to INMUNOVA or its designee or affected to another destination (i.e., destroyed at the centre at the direction of INMUNOVA or its designee) during the course of the study and at the time of its completion. The IMP should be administered to subjects only by suitably qualified staff. The IMP must be used in accordance with the provisions of the protocol and by persons under the direct supervision of the investigator. Investigators must maintain records that adequately document the fact that subjects received the protocol-specified dose of IMP and that a reconciliation of all IMP received at the centre is made prior to final disposal. Upon completion of the study, or as indicated, all IMP, including unused, partially used or empty containers will be returned to INMUNOVA or its designee, or destroyed at the centre at the direction of INMUNOVA or its designee.

8.5 Concomitant medication

All prescription or over-the-counter medications (e.g. over-the-counter medications and dietary supplements) that subjects refer as a medication they have taken within the 7 days prior to Screening (V1) will be evaluated and recorded on that visit. For each drug, the documentation must document the generic name or the name or brand name, the total daily dose, including the units (or the scheduled and actual dose, units and frequency of administration in the event that the medication is not administered on a daily basis), the route of administration and the reason for its use.

Concomitant medication refers to all drugs and treatments used within the period between signing the IA/CF prior to screening and the end of participation in the study.

Medication changes, additions, and discontinuations will be evaluated and recorded in the CRF during each study visit. All prescriptions given on demand (*pro re nata*) should be converted to reflect the actual number of tablets or doses received per day.

8.5.1 Allowed concomitant medication

The treatments considered necessary for the well-being of the subject may be indicated according to the criteria of the study clinician. If the permissibility of a certain drug/treatment is in doubt, INMUNOVA or its designee should be contacted to resolve the issue.

8.5.2 Prohibited concomitant medication

The treatments considered necessary for the well-being of the subject may be indicated according to the criteria of the study clinician. If the permissibility of a certain drug/treatment is in doubt, INMUNOVA or its designee should be contacted to resolve the issue. All treatment with a therapeutic objective against SARS - CoV-2 must be reported to the medical monitor.

8.6 Compliance with the treatment regime

Administration of the IMP will be supervised by study staff to ensure adherence to the treatment regimen.

8.7 Study drug discontinuation criteria

1) The study medication must be discontinued if:

- In the event of a severe hypersensitivity phenomenon (allergic reaction ≥ grade 3 and/or anaphylaxis), the study drug will be immediately discontinued and standard support and treatment measures will be implemented. The subject will continue with the visit schedule as established by the protocol.

- In the event that a subject has received the first dose of study drug without having met the criteria for entering the protocol. The study medication should be discontinued, i.e., the next dose will not be administered. The reason for discontinuation must be recorded in the medical record and in the CRF. The subject will continue with the safety controls complying with the schedule of the follow-up visits and will carry out the V8 (ET) 4 weeks after the last dose as indicated in Section 8.7. This subject will not perform procedures related to taking pharmacokinetic samples at these visits.

- In the event that the subject/legal guardian of a subject who received the first dose of study drug refuses the administration of the second dose, the study medication should be discontinued, that is, the next dose will not be administered. The reason for discontinuation must be recorded in the medical record and in the CRF. The subject will continue with the visit schedule as established by the protocol.

2) The investigator will decide, per his/her medical criteria, if the study drug is discontinued in the following cases:

- In the event of a Grade 1 or Grade 2 allergic reaction (infusion-related reaction). The investigator will provide symptomatic treatment and decrease the infusion rate or interrupt the infusion. The investigator must document the decision taken and any change in the administration of the study drug in the patient's medical history accordingly. In the event the physician determines to discontinue the study medication, the next dose will not be administered. The reason for discontinuation must be recorded in the medical record and in the CRF. The subject will continue with the visit schedule as established by the protocol.

- In the event that clinical and/or laboratory events are detected in a subject that make the investigator, per his/her medical criteria, consider that the discontinuation of the medication is the most convenient for the subject. The study drug should be discontinued, i.e., the next dose will not be administered. The reason for discontinuation must be recorded in the medical record and in the CRF. The subject will continue with the visit schedule as established by the protocol.

9 ADVERSE EVENTS

Throughout the entire study, all AEs will be monitored and recorded in an AE eCRF, including the AE description, start and end date, seriousness, severity, action taken and relationship to IMP. In the event of an AE, the priority will be the safety of the study subject.

According to the ICH E2A guideline (80): An AE is any unforeseen and unwanted medical event that occurs in a patient or clinical research participant who has been administered a pharmaceutical product, which does not necessarily have to have a causal relationship with such treatment. Therefore, an AE can be any unfavourable and unwanted sign (such as an abnormal laboratory finding) or symptom, or disease, temporarily associated with the use of a medicinal product, regardless of whether it is considered related to the drug medicinal product.

According to the National Administration of Medicines, Food and Medical Technology (ANMAT) (81): any adverse clinical event that occurs in a patient or a subject of a clinical research study to which a pharmaceutical product has been administered or has been performed a therapeutic procedure and that does not necessarily have to have a causal relationship with the treatment. Therefore, an AE can be any sign (including an abnormal laboratory finding) or symptom, unfavourable or unintentional, or disease, that has a temporal association with the use of the investigational medicinal product, regardless of whether or not it may be related to the same.

Medical interventions, such as surgeries, diagnostic procedures and therapeutic procedures are not AE, but they are the measure taken to treat the clinical condition. All of them must be registered as treatments for AE.

9.1 Documentation of adverse events

All AE that occur within the period from the moment the subject or the subject's guardian signs the CF until the last study procedure is carried out will be recorded. All AEs that occur prior to the start of treatment (i.e. before the 1st. dose of the IMP) will be recorded as a medical history. Likewise, if the sign, symptom or disease was already present before the start of the treatment period, it will only be considered an AE in the event that it worsens after the start of the treatment period. Investigators must document all significant illnesses the subject has had within the 3 months prior to the Screening Visit. Additional pathologies that were present at the time of informed consent should be considered concomitant diseases. Pathologies that occur or are detected for the first time during the study, and/or concomitant conditions that worsen during the study, must be registered as AE in the eCRF.

All clinical laboratory results, vital signs, and ECG results or findings should be evaluated by the investigator for their clinical significance. Isolated abnormal findings in clinical laboratory tests, vital signs or ECG (i.e., not part of an informed diagnosis) should be reported as AE if they are symptomatic, lead to discontinuation of the study drug or a dose reduction, require corrective treatment or constitute an AE as determined by the investigator based on clinical judgment.

At each designated time point, the investigator will determine whether any AE has occurred by evaluating the subject. AEs can be observed directly, or they can be spontaneously reported by the subject or detected in the questioning of the subject at each time point. Open-ended questions should be used to interrogate the subject, requesting information in a general way without specifically mentioning any particular symptoms. The investigator must evaluate all AEs for intensity, causality, and seriousness, according to the definitions given in Sections 9.2, 9.3 and 10.1, respectively. The investigator's assessment must be clearly documented in the source documentation of the study centre, which must also include the signature of the investigator.

The diagnosis in all cases should be reported using the term AE or SAE. In cases in which there is no diagnosis, the primary sign or symptom should be reported using the AE or SAE term along with additional data in the narrative report until it is available at the diagnosis. If

the signs and symptoms are independent and do not suggest a common diagnosis, they should be reported as individual AE or SAE reports.

The investigator must report all AEs on the eCRF AE screen and source documents, regardless of seriousness, severity, and causality. Whenever possible, AE will be reported using a diagnostic term, (e.g. “common cold” or “upper respiratory infection” rather than “nasal congestion, cough, and low-grade fever”), and will be described with the attributes listed in Sections 9.2 and 9.3.

9.2 Assessment of intensity

Each AE will be classified according to the following criteria:

Mild:	AE does not significantly interfere with the subject's normal performance level.
Moderate:	AE generates some deterioration in performance but does not imply a risk to the subject's health.
Severe:	AE generates a significant deterioration in performance or is disabling, and constitutes a clear risk to the subject's health.

Severity vs. seriousness Severity is used to describe the intensity of a certain event, whereas the event itself may be of relatively minor medical significance (such as, for example, a severe headache). This is not the same as "seriousness", which is a concept that is based on the outcome of the event/subject at the time of the event.

When changes in the intensity of an EA occur more than once in the course of the same day, the maximum intensity of the event must be recorded. If the intensity category changes over several days, these changes must be recorded separately (with separate start dates).

9.3 Assessment of causality

Each AE will be ranked based on its relationship to the IMP, based on the criteria outlined below. Although the attribution of causality made by the investigator will be collected for the reported events, for analytical purposes the existence of a temporal association with the use of the IMP will be presumed sufficient for there to be at least one plausible association.

Not related:	There is no causal relationship between the IMP and the AE, and there is an obvious alternative cause, e.g. concomitant treatment or subject's underlying condition.

Possibly related:	A relationship with the administration of the IMP seems unlikely, but cannot be ruled out with certainty. An AE may be considered possibly related if, or when, it meets 2 of the following criteria: (1) it follows a reasonable time sequence with respect to the administration of the IMP; (2) it is not a consequence that is to be expected in view of the subject's clinical condition or environmental or toxic factors or other forms of therapy administered to the subject; or (3) it follows a known pattern of response to PMI but does not reappear on repeat exposure or there is a cause that is more likely.
Related:	There is a reasonable/plausible chance that the AE may have been caused by the IMP.

When evaluating the relationship with the IMP, the following criteria will be taken into consideration:

- Known effect of the pharmacological class.
- Biological plausibility.
- Lack of an alternative explanation associated with a pathology or concomitant medication.

Additionally, alternative causes of AE (not related to IMP) will be evaluated, such as: concomitant medication, study disease, study procedure or other medical conditions.

9.4 Action taken in relation to the study drug

- Dose unchanged: No change was done to the dosage of the study drug.
- Drug withdrawn: The study drug was interrupted definitively.
- Drug interrupted: The study drug was temporarily suspended.
- Not applicable: The subject died, study treatment had been completed prior to the reaction/event, or the reaction/event occurred before the start of the treatment.

9.5 Other action taken in relation to the event

- None (this is, no treatment was necessary).

- Required medication (this is, over the counter and/or prescription drugs were needed to treat the AE).
- Required hospitalisation or the prolongation of an existing hospitalisation (that is, the patient had to be admitted, or their hospitalisation had to be prolonged, as a consequence of the AE, regardless of whether or not medication was required).
- Other

9.6 Result of the adverse event

- Recovered/resolved (this is, subject fully recovered from AE with no residual effect observed).
- On the mend/on the way to resolution (that is, the AE improved but has not been fully resolved).
- Unrecovered/not resolved (that is, the EA itself is still present and manifest).
- Recovered/resolved with sequelae (that is, residual effects of the AE continue to be present and manifest, including sequelae/residual effects).
- Fatal (the event had a fatal outcome; this term should be used when death occurs as a direct result of AE).
- Unknown

9.7 Changes in the parameters of the clinical laboratory

Any abnormality in a laboratory value that occurs for the first time or that has worsened in terms of severity or frequency with respect to the baseline status and that meets 1 of the following criteria will be recorded in the AE pages of the eCRF:

- Requires therapeutic intervention or diagnostic tests
- Leads to IMP interruption
- Occurs accompanied by, or induces, signs or symptoms
- Is clinically significant at the discretion of the investigator

Combined elevations of aminotransferases and bilirubin, whether serious or not, and regardless of whether or not they are causally related, that meet the criteria for a potential case of Hy's Law (total bilirubin level ≥ 2 × ULN simultaneously accompanied by ALT or AST values ≥ 3 × ULN) should always be reported to the sponsor as soon as possible after performing the procedures detailed in Section 10.2 for the SAE report, and submitted along with the investigator's assessment of seriousness and causation and a detailed narrative report.

9.8 Overdose

Any instance of overdose must be reported to INMUNOVA or its designee or a person specifically designated for that purpose within 24 hours, and must be fully documented as an AE or as an SAE in the event that it meets the SAE criteria. The details of the signs or symptoms and their management should be recorded, including details of the antidote(s) administered.

9.9 Adverse events of special interest

An AESI is an AE (serious or non-serious) that raises concern from a medical or scientific point of view, that is specific to the study drug, and for which continuous monitoring and immediate notification by the investigator to INMUNOVA or its designated (see page) is required. These AE may require additional research to characterize and understand them.

- Injection site reactions
- Hypersensitivity reactions

9.10 Follow-up of adverse events

All AE will be followed-up up to its resolution or stabilisation, and its result (outcome) must be documented in the eCRF.

If the investigator detects an AE in a study subject after the last scheduled follow-up visit and considers that the event is possibly related or related to the study treatment received, the investigator should report this event to INMUNOVA or its designated representative.

10 SERIOUS ADVERSE EVENTS

10.1 Definition of serious adverse events

A SAE is any event that meets any of the following criteria:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongs existing hospitalisation
- Results in significant or persistent incapacity/disability
- It is a congenital anomaly or birth defect that develops in a child who has been fathered/conceived by a subject who received IMP.
- Other: Major medical events that do not lead to death, are not life-threatening, or do not require hospitalisation may nevertheless be considered an SAE when, based on appropriate medical judgment, they may endanger the subject and may require medical or surgical intervention to avoid any of the outcomes mentioned in this definition. Examples of such events are the following:
    - Intensive treatment in the emergency room or at the subject's home for allergic bronchospasm
    - Blood dyscrasias or seizures that do not lead to the patient’s hospitalisation
    - Development of drug dependence or abuse

Definition of terms

Is life-threatening: an AE is life threatening if the subject was in imminent risk of death from the event as it occurred; that is, it does not include a reaction that, had it been more severe (serious), could have caused the death of the patient. For example, drug-induced hepatitis that resolved without evidence of liver failure would not be considered a life-threatening event, even though such an event could result in death.

Hospitalisation: AEs that require hospitalisation should be considered SAE. Hospitalisation for elective surgery or routine clinical procedures that are not caused by an AE (e.g. elective surgery for a pre-existing condition that has not worsened) is not considered an AE or an

SAE. In any case, if the occurrence of an unforeseen and unwanted event is reported during the procedure, it must be reported as an AE, either "serious" or "not serious", according to the usual criteria.

In general, hospitalisation means that the subject has been admitted (which usually involves at least one overnight stay) in the hospital institution or in the emergency room for observation and/or to receive treatment that could not be administered in the doctor's office nor on an outpatient basis. In the event that there is doubt as to whether what is considered a “hospitalisation” has occurred or whether it was necessary, the AE should be considered serious.

Regarding death events, in all cases it should be reported as an SAE.

Any unforeseen and unwanted event that is serious, that occurs after the reporting period, and that, in the investigator's discretion, is an event related to the study drug must also be reported and handled as an SAE.

The investigator should follow up with subjects with AE until the event has resolved or the condition has stabilised. If there is no resolution of any of the AE, which includes significant clinical laboratory abnormalities detected in the EOS assessments, these events will be followed until they are resolved or until they are no longer clinically relevant.

Disabling/incapacitating: An AE is incapacitating or disabling if it leads to a substantial and/or permanent impairment of the subject's ability to carry on her life normally.

10.2 Notification of serious adverse events

Each AE will be evaluated to determine whether it complies with the seriousness criteria (Section 10.1). If the AE is considered serious, the investigator must notify such event to INMUNOVA or its designee and to the Institutional Review Board (IRB) or the Ethics Committee (EC) in accordance with their standard operating procedures.

The events that at the investigator's discretion are considered progression of the COVID-19 disease are part of the primary and secondary data set used for the study's efficacy analyses, and therefore will not be considered as an AE, will not be registered as a SAE in the clinical study safety database and will not be notified to regulatory authorities under expedited modality.

If the investigator detects a SAE in a study subject within 30 days of the last scheduled product application, and considers that the SAE is related or possibly related to the administration of the study IMP, the investigator should report such event to INMUNOVA or its designee.

The investigator must report all SAEs to the sponsor using the SAE form within 24 h of becoming aware of the event, regardless of their relationship with the study drug. You should send it to the following email box: Farmacovigilancia@latresearch.com. Additionally, he/she will document the SAE in the AE form in the eCRF of the corresponding subject.

All information regarding the SAE will be collected and reported through the SAE form. The investigator must send the initial report within 24 h of becoming aware of the SAE. At a minimum, the initial report should include the following information:

- Event
- Study code
- Subject code
- Date of administration of the IMP
- Name and contact information of the person reporting the event

If the SAE has not been resolved by the time the investigator submits the initial SAE report, the investigator must provide a follow-up report as soon as the event is resolved (or when significant information is received in the event that the event is still is in progress). Additional follow-up information must be reported through the SAE form within 24 h after the investigator (or site staff) becomes aware of it. The investigator should not delay the SAE report to wait for additional information. Additional information, when it arises, must be reported in accordance with the aforementioned notification procedures.

All SAEs should be followed up until they resolve, until the condition stabilizes, until the subject is lost, or until an alternative explanation for them is found. Once the SAE has been resolved, the centre staff must send an updated SAE form, as well as update the eCRF AE form corresponding to the subject. Likewise, in the event that there is a relevant laboratory report, the reports of consultation with other health professionals, discharge reports or other information that has been collected in relation to the event must be transmitted to the sponsor.

In the case of a “minimum report” (that is, a report that contains only the information mentioned in the previous bullets), a more detailed follow-up report should be sent as soon as more information emerges in this regard, always without exceeding a period of 7 calendar days from the date of the initial report. Each SAE must be followed up until its resolution or stabilisation, and in the case of reported deaths, the investigator must provide INMUNOVA or its designee and the IRB/EC with any additional information that they request (e.g. reports of autopsy and final medical reports).

The sponsor or its representative will be responsible for determining and, in turn, reporting the SAE to regulatory authorities in accordance with the relevant regulatory requirements.

11 STATISTICS

11.1 General procedures

Statistical analysis will be performed by INMUNOVA or its designee in collaboration with INMUNOVA. A detailed SAP will be finalised and signed prior to closing the database and prior to the opening of the study masking. All deviations that occur with respect to the analyses described below will be included in the SAP, which will be incorporated into the Clinical Study Report (CSR). The CSR will be written after all subjects have completed the 28-day follow-up and the primary efficacy analysis and secondary efficacy analysis have also been completed.

11.2 Analysis set

The Full Analysis Set (FAS) will be made up by all the randomised subjects to the IMP.

The modified intent-to-treat group will be made up of all subjects who have been randomised to receive the IMP and who have received the full treatment regime of the IMP. This population will be the basis on which all efficacy analyses will be performed.

The Per Protocol population will be made up by all the subjects in the mITT who have no major protocol deviations. Major protocol deviations will be reviewed and subjected to determination prior to closing the database and the unblinding. The PP population will be used for the endorsement sensitivity analysis.

The Safety Population will be made up of all subjects who have received at least 1 dose of the IMP. This population will be used for all summaries of accounting data, baseline and demographic characteristics of subjects, and safety information, including incidence of AEs.

11.3 Determination of the sample size

The purpose of the primary efficacy analysis is to demonstrate the superiority of INM005 compared to placebo, based on an absolute reduction of 15% in the incidence of the event of primary interest, that is, a reduction of 2 orders on the severity scale. of illness or discharge in the treated cohort within 28 days (82).

Assuming a 70% “standard of care” event rate (Wang 2020, https://doi.org/10.1016/S0140-6736(20)31023-0) and an absolute effect size of 15 percentage points, for a power of 80%

and an error $\alpha = 0.025$ (for a one-tailed comparison), 121 subjects will be required in each treatment group, totalling 242 participating subjects.

11.4 Randomisation

Using a randomisation sealed envelope system, approximately 242 subjects will be assigned to treatment throughout the entire study span in a 1:1 ratio. Randomisation will be carried out in blocks of 4 and 6 subjects, stratified by participating site.

11.5 Statistical methods

11.5.1 Efficacy analysis

11.5.1.1 Primary and secondary analysis

The differences between patients in both treatment groups in the proportions of the primary and secondary efficacy endpoints will be analysed using the Chi-square test. The differences between these groups in the endpoints that involve the time to the occurrence of the events will be analysed using the non-parametric Mann-Whitney test (83).

For the pharmacokinetic analysis, a non-compartmental model will be used. A population pharmacokinetic analysis will be performed using a non-linear mixed effects model (84).

11.5.1.2 Exploratory analysis

Anti-SARS-CoV-2 antibody levels will be compared using a Levene's fit T test, if necessary. A descriptive analysis will be performed for the presence of anti-drug antibodies.

The change in laboratory variables will be compared in those patients in whom disease progression is recorded or not by parametric or non-parametric tests, as appropriate. Variables with significant differences or those that are considered biologically relevant will be included in a multivariate logistic regression model. The presence of multicollinearity will be ruled out (83).

11.5.2 Safety analysis

11.5.2.1 Adverse events

AEs will be coded by PT (Preferred Term) using the Medical Dictionary for Regulatory Activities (MedDRA) classification. All AEs reported with an onset or worsening after administration of study medication will be included in the analysis. The incidence of AE will be summarised by treatment group and by severity and relationship with the study drug. Serious AE and AE leading to withdrawal from the study will be tabulated.

A treatment emergent adverse event (TEAE) is defined as an AE that starts simultaneously with or after the administration of the study drug dose, or a pre-existing condition that has worsened simultaneously with or after the administration of the dose of the study drug.

The incidence of TEAEs and treatment-related AE will also be summarised by maximum severity and by the highest degree of relationship to IMP according to the main system organ class and MedDRA preferred term. This summary will include the total number and the percentage of subjects who report a certain event. In counting the number of reported events, an uninterrupted event, that is, one that is reported on more than one occasion and that did not cease, will be counted only once; AE that are not continuous and that are reported multiple times in relation to the same subject will be counted as multiple events.

11.5.2.2 Laboratory data

Laboratory data (haematology parameters, blood chemistry and urinalysis) will be presented for each treatment group using descriptive statistics parameters, which include the mean and mean values of the change from baseline at each stipulated time point. on the schedule. Displacement tables will be generated in which the number of subjects with normal/abnormal values at baseline versus post-treatment will be presented. The frequency of laboratory abnormalities will be tabulated. In the data lists ordered by subject, laboratory values that are not within the normal reference ranges and markedly abnormal findings will be marked with an alert.

11.5.2.3 Vital signs

Changes from baseline in vital signs, SBP (systolic and diastolic), body temperature, pulse, and respiratory rate will be summarised for each treatment group using descriptive statistics. The last measurement obtained prior to administration of the study drug will serve as the baseline level. The percentage of subjects with values outside the clinically important limits

will be summarised. A list of the values of body weight, height and BMI registered in the Screening (V1) will be provided.

11.5.3 Demographics and baseline

The treatment groups will be compared in terms of the demographic characteristics of the subjects, and the baseline characteristics will be summarised using descriptive statistics; tests will not be performed by formal statistical analysis.

11.6 Blinded safety data review

The safety data (including demographic characteristics, disease characteristics, AE, AESI, vital signs, hematology, biochemistry) obtained from the Safety Cohorts (every 12, 24, 48, 96, 192 enrolled patients) will be examined low masking by the DMC. The data will be presented using fictitious subject numbers in order to preserve masking.

The Argentine Regulatory Agency (ANMAT) will be notified and the DMC reports will be presented accordingly.

11.7 Interim analysis

An interim analysis will be carried out after 60% of recruitment has been reached; that is, approximately after the end of the follow-up of the first 145 subjects. The Data Monitoring Committee will analyse the event rate in the group under the SoC and may recommend: (1) modifying the sample size, based on the observed event rate, or (2) stopping the study if: (2.a) it’s considered that it is not feasible because it requires an excessively large sample size or (2.b) it’s considered futile because of an event rate ≥ 95%.

The re-estimation of the sample size will allow the sample to be increased by up to 72 subjects, to reach 314 subjects. The requirement of a greater number of subjects would be considered "Not Feasible" and will cause the study to be stopped.

11.7.1 Data monitoring committee

A DMC will periodically review and evaluate the accumulated study data regarding the safety of the subjects, the conduct and progress of the study, and, if relevant, the efficacy throughout both stages of the study. The DMC will issue recommendations regarding the continuation,

modification or interruption of the study in a process in which the highest priority will always be to guarantee the safety of the participants. The composition, the frequency of the review, the range of decisions allowed and the methods for the disclosure of the information are matters that will be addressed in a separate statute that will be in line with the guidelines that have been issued for other studies of continuous adaptive design (ASD).

The DMC will determine if the study can be continued based on the safety findings (i.e., “there are no safety observations that warrant permanent cessation of subject recruitment” or “safety observations warrant permanent cessation of enrolment of subjects”).

To maintain data integrity during interim analysis, use of a DMC will be used to make decisions regarding pre-specified study adaptations in relation to sample size estimation and premature study discontinuation for reasons of futility or overwhelming efficacy. Pre-specified accommodations, as well as committee rules applicable to interpretation and decision-making regarding accommodations, will be defined in the DMC Charter. Next, the framework for the organisation of the DMC statute is provided, as well as biostatistical approaches to adaptations.

The DMC Charter will define all the responsibilities, functions, composition, structure of meetings, communications, the Statistical Analysis Plan (SAP) of the DMC and the rules for decision-making. This document will be generated by the sponsor and will be presented for review after an organisational meeting, which will take place prior to the recruitment of the first subject. The organisational meeting will be attended by the members of the DMC, the director of the DMC, the study statistician, the unblinded statistician, the members of the pharmacovigilance team and a representative of the sponsor who will act as a link with the DMC. This meeting will be used to familiarize the DMC with the study protocol and to finalize the DMC Charter. Subsequently, the DMC will convene an open and closed data review session, as described in the Charter. The sponsor's representative may participate in open sessions to provide a report regarding the progress of the study, and to request advice and approval for amendments to the protocol, changes to the informed consent, or updates to the investigator's manual. The minutes of the open sessions generated by the Chairman of the DMC will be available to the sponsor's representative. The minutes of the closed sessions of the DMC will be kept within a confidentiality framework. The DMC Chairman will also have the prerogative to schedule ad hoc meetings for safety-related issues that may arise and warrant them. These meetings may be held without the sponsor's knowledge of their holding; however, in the event that they occur with the knowledge of the sponsor, the latter may not

have knowledge of the agenda of the day. Additional details about the communication process and data flow will be provided in the DMC Charter.

This Charter will be organised in accordance with the directive documents for the organisation of the DMCs, and will be subject to regulatory review prior to the start of the clinical study. In accordance with regulatory guidelines regarding the role of DMC in adaptive designs, the DMC will not recommend or make changes to adaptive design once the DMC has access to data encoded by treatment or data that has been completely unblinded.

11.7.2 Futility in the interim analysis

Assuming that the safety data is permissive, the determination of futility in the interim analysis will be evaluated by the DMC. Futility is concluded when the rate of events in the standard therapy arm is greater than or equal to 95%.

All analyses will be carried out by the DMC, and the charter of the DMC will be explicit regarding the composition of this committee, the methods for reviewing the data, and the possible decisions that might arise from such review.

12 ETHICAL CONSIDERATIONS AND RESPONSIBILITIES

12.1 Good Clinical Practice

The study will be carried out in accordance with the provisions of this protocol, the ICH Good Clinical Practice (GCP) guidelines (85), the regulations relating to electronic records and electronic signature and the most recent versions of the guidelines of the Declaration of Helsinki (86) and the regulatory regulations applicable in Argentina (81). These guidelines are on file at INMUNOVA.

12.2 Data monitoring committee

A DMC will periodically review and evaluate the accumulated study data regarding the safety of the subjects, the conduct and progress of the study, and, if relevant, the efficacy throughout both stages of the study. The DMC will issue recommendations regarding the continuation, modification or interruption of the study in a process in which the highest priority will always be to guarantee the safety of the subjects. The composition, the frequency of the review, the range of decisions allowed and the methods for the disclosure of the information are matters that will be addressed in a separate charter. The DMC will appoint a subcommittee that will be in charge of reviewing the safety data of the Safety Cohort.

DMCs have traditionally been used to independently monitor studies for patient safety and to determine the risk-benefit ratio within studies. However, there is the possibility that the DMC may be asked to also issue pre-specified study adaptations, such as those envisaged in the proposed study in relation to dose selection, sample size estimation, and premature discontinuation of the study for reasons of futility or efficacy. The responsibilities of the DMC and the rules for decision-making will be defined in the DMC Charter (87-88).

In the proposed study, the DMC will function as an independent review committee in that its members will be considered independent of the sponsor and of any provider contracted by the sponsor. Likewise, both INMUNOVA and the clinical study team will be limited in their access to the open parts of the DMC sessions, in which data such as recruitment, compliance with the treatment regimen, and study withdrawals, and study withdrawals, may be reviewed, cumulative AE rates, although not separately for each branch of the study. The DMC members must preserve the confidentiality of all study communications, including reports, data, review session discussions, conference calls, and session minutes, to ensure that no information is disclosed to the INMUNOVA clinical study team, INMUNOVA (with the exception of open reports), or third parties. An unblinded statistician, who will not be part of

the DMC, will act as a liaison between the sponsor and the DMC and will provide periodic presentations of efficacy and safety data for review by the DMC. The medical representative of INMUNOVA will be the one who receives the recommendations made by the DMC to INMUNOVA. The specific procedures to be used for interactions between DMC members and non-DMC individuals (i.e. the unblinded statistician, INMUNOVA, or any supplier contracted by the sponsor) will be defined in the DMC Charter.

12.2.1 Members of the Data Monitoring Committee

The DMC for this study will be made up of a minimum of 3 members, of whom one must have training in biostatistics. Members of the DMC will be appointed by INMUNOVA, and selected from the medical community based on their expertise in the area of interest and their expertise in biostatistics. All members of the DMC must also have experience in conducting clinical studies. Although formally he is not a member of the DMC, the non-blind biostatistician is essential in the communication of the study data to the DMC and, therefore, must be a person with experience in interim analysis of data from clinical studies. The members of the DMC will not be involved in the design of this study or its conduct, except through their role in the DMC, and may not have any significant financial or other relevant relationship with the sponsor. All members of the DMC must be present at the sessions for a quorum to be reached. Likewise, 1 member of the DMC will serve as the Chairman of such committee and will be responsible for presiding over the DMC sessions and preparing the minutes of the closed sessions, and will assume responsibility for all communications exchanged between the DMC and the sponsor. The roles and responsibilities of all members will be defined in the DMC Charter.

12.2.2 Generation of the Data Monitoring Committee Charter

The DMC Charter is a fundamental document that defines all the responsibilities, functions, composition, structure of meetings, communications, the Statistical Analysis Plan (SAP) of the DMC and the rules for decision-making. This document will be generated by the sponsor. Prior to the recruitment of the first patient, an organisational meeting will be held. The organisational meeting will be attended by the members of the DMC, the director of the DMC, the study statistician, the unblinded statistician, and the members of the pharmacovigilance team. This meeting will be used to familiarize the DMC with the study protocol and to finalize the DMC Charter.

12.2.3 Data Monitoring Committee Meetings

The meetings will consist of open or closed sessions. In open sessions, only blind safety information will be dealt with, and the content of such sessions will be coordinated by the non-blind statistician. Only members of the DMC and the non-blind statistician may attend the closed sessions; in these sessions, the non-blind statistician will present the reports that are specifically programmed for the members of the DMC. These reports, which will be partially or totally blinded, will be grouped and presented by treatment group, but the names of the treatments in question will not be released. The non-blind statistician will not be present for the remainder of the DMC's deliberation, unless requested to do so by the DMC members. Likewise, ad hoc meetings may be held as required; the rules for such meetings will be defined in the DMC Charter.

12.2.4 Role of the Data Monitoring Committee in adaptive designs

The DMC considerations are highlighted in the US FDA guideline for adaptive design studies (53). While most of the recommendations provided in such a guideline have been highlighted in the preceding paragraphs, key considerations regarding DMC and adaptive designs are outlined. As mentioned above, the DMC can be prospectively selected to implement decisions regarding pre-specified study adaptations, in addition to performing its role in relation to safety monitoring. This guideline states that “In those cases in which adaptations are based on interim analyses of unblinded results, robust, pre-specified and well-documented procedures must be in place before the clinical study or data review can begin” (53). The content of this guideline underlines the importance of the DMC Charter in establishing the rules for adaptation within the framework of the study.

In all studies involving a DMC in which the data is not protected by blinding, the integrity of the data is critical. Due to the nature of the analysis and the ability to influence the study based on interim data, this guideline emphasizes the critical nature of creating protection/safeguards mechanisms that allow the sponsor to remain unaware of unblinded data or any other influence that might arise from the interim data. Similarly, the guideline states that both researchers and study subjects should receive as limited information as possible regarding the extent of possible adaptive changes. Once again in this case, the DMC Charter plays a fundamental role in establishing the procedures by which the DMC will govern to evaluate the interim analysis and communicate adaptations.

Finally, the FDA guideline on adaptive designs indicates that the DMC will not be able to recommend or make changes to the adaptive design after having had access to data encoded

by treatment or data that has been completely unblinded, since that such recommendations could lead to loss of data integrity.

12.3 Steering Committee

No Steering Committee will be used for this study.

12.4 Institutional Review Board/Ethics Committee

The study must be approved by a duly constituted IRB/EC. Such approval is required for the study protocol, protocol amendments, AF/CFs, subject information sheets, and publicity materials. The IMP will not be sent to the site until the Sponsor or its representative has received the written authorisation issued by the IRB/EC.

12.5 Informed consent

For each study subject, a written AF/CF will be obtained prior to carrying out all activities related to the protocol. As part of this procedure, the investigator or a designated representative will deliver the AF/CF document to the subject, after which they must orally explain the nature, duration, and purpose of the study and the action of the IMP in such a way that the subject and the parent(s) or guardian are aware of the potential risks, annoyances or adverse events that could arise. Subjects should be informed of the possibility of withdrawing from the study at any time they wish. They will be provided with all the information required by local regulations and ICH guidelines. The Principal Investigator or a designated representative will provide the sponsor or his representative with a copy of the AF/CF approved by the IRB/EC/health authority prior to the start of the study.

The informed consent form must contain, at a minimum, the elements of consent described in the ICH Good Clinical Practice (GCP) guideline. INMUNOVA or its designee will review a copy of the AF/CF intended for use to determine its acceptability; this document must be presented by the investigator or his/her designee, together with the protocol, to the corresponding IRB/EC for its due review and approval before the study begins at the research centre. The assent/consent forms must be written in such a way that they are fully comprehensible for the future subject. The investigator must provide the sponsor or his/her designee with a copy of the approval letter issued by the IRB/EC regarding the protocol and AF/CF before the study drug supplies can be dispatched and the study can begin.

The assent/consent forms should be modified in the event that new information emerges during the study that could be relevant to the subject. Any modification must be presented to the corresponding IRB/EC for its due review and approval before it can be implemented.

A copy of the signed informed assent form and informed consent form must be given to the subject, and the original copies of these documents must be kept in the designated location within the study centre.

Before starting any of the study procedures, it will be the responsibility of the investigator or his/her designee to obtain informed consent after an adequate explanation of the objectives, methods and anticipated benefits and potential risks of the study. The subject should be given sufficient time to make a decision regarding study participation, as well as the opportunity to ask questions about the particular issues in the study. The AF/CF approved by the IRB/EC must be signed and dated in handwriting by the subject and by the person in charge of carrying out the explanation of the informed consent. The investigator or appropriate centre staff should document the details of obtaining informed assent/consent in the subject's study documents.

12.6 Records management

By signing this protocol, the investigator grants his/her permission for the sponsor's staff, their representatives and the corresponding regulatory authorities to carry out on-site monitoring of all the corresponding study documentation, on physical (paper) or electronic media, as well as on-site reviews of the procedures used to generate eCRFs, if clinically relevant.

12.7 Source documents

Note that there will be various original documents, data, and records that will be considered source documents in this study. The eCRF itself cannot be used as a source document under any circumstances.

12.8 Study records and record retention

The investigator must make arrangements for the retention of study records at the centre. The nature of the records and the length of the retention period must comply with the requirements of the relevant regulatory authority. The investigator must take steps to prevent accidental or premature destruction of such documents

13 AUDITS AND MONITORING

This study will be subject to quality assurance monitoring at all stages of its development by the clinical research staff employed by the sponsor or its representative. This monitoring will include in-person visits, remote monitoring, and telephone communications designed to ensure that the investigation is being conducted in accordance with protocol, standard operating procedures, GCP guidelines, and relevant regulatory requirements. Quality control procedures will be applied to each stage of data management to ensure that all data is reliable and has been processed correctly. The on-site review of the eCRF will include a review of the forms in order to confirm that the information contained in them is clear and complete and agrees with what is contained in the existing source documents for each subject.

There is the possibility that medical advisers or clinical monitors (clinical research associates, CRAs) or clinical trial assistants might request to witness the subject assessments that are performed as part of this protocol. The investigator and the corresponding staff will be requested periodically to attend the meetings/workshops organised by the sponsor, in order to ensure proper execution of the protocol. The study may be subject to audits by the sponsor or the regulatory authorities. If such an audit occurs, the investigator must provide access to the subject's records as necessary. By signing this protocol, the investigator grants his/her permission for the sponsor's staff, their representatives and the corresponding regulatory authorities to carry out on-site monitoring of all the corresponding study documentation, as well as on-site reviews of the procedures used to generate eCRFs, if clinically relevant.

14 AMENDMENTS

Modifications to the protocol, with the exception of those intended to reduce an imminent risk to study subjects, may only be made by the sponsor. Any change in the protocol intended to avoid an obvious imminent risk to the subjects may be implemented immediately, subject to the condition that the IRB/EC is notified of this within a period of 5 days.

Modifications to the protocol that are permanent in nature should be handled as an amendment to the protocol. The written amendment generated must be submitted to the IRB/EC, and the investigator must wait to receive the corresponding approval before implementing the changes. The sponsor will present the amendments to the protocol to the corresponding regulatory authorities for their corresponding approval.

If the amendment to the protocol, at the discretion of the IRB/EC, the investigator and/or the Sponsor, substantially modifies the study design and/or increases the potential risk for the subject and/or has any repercussion on the subject's involvement as a subject. of the study, the AF/CF in writing in force will require a modification of the same content. In such cases, the informed consent of those subjects who are enrolled in the study must be renewed, before they can continue with their participation.

15 STUDY REPORT AND PUBLISHING

The Sponsor is responsible for preparing and supplying the relevant regulatory authorities with the Clinical Study Reports (CSR) in accordance with the corresponding regulatory requirements.

The sponsor's publication policy is discussed in the Clinical Research Agreement entered into with the investigator.

16 INTERRUPTION OF THE STUDY

Both the sponsor and the Principal Investigator reserve the right to definitively interrupt the study at the investigator's centre at any time they deem it appropriate. If necessary, the sponsor or a specified designee will inform the corresponding regulatory authorities about the definitive discontinuation of the study and the reasons for such decision, and the Principal Investigator will inform the IRB/EC about it. In the event of a definitive interruption of the study, the sponsor and the Principal Investigator will guarantee due consideration of the safeguarding of the subjects' interests.

17 CONFIDENTIALITY

All the information generated in the framework of this study is considered highly confidential and cannot be disclosed to any person or entity that is not directly involved with the study, unless there is prior written consent from the sponsor authorising such disclosure. Notwithstanding this, the officials of the authorised regulatory authorities, the staff of the IRB/EC, the sponsor and their authorised representatives have the right of full access to the records.

The identification of the subjects and the eCRF will be carried out only by means of the screening and treatment numbers. If requested, the full name of the subject may be made known to an authorised regulatory entity/agency or other official or person in charge authorised for this purpose.

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APPENDICES

Apéndice 1. Names[NB3] of the members of the study staff

The list of the team members is provided in a separate document.

Apéndice 2. Guidelines[NB4] for the management of an anaphylactic reaction

Hypersensitivity reactions and severe hypersensitivity reactions, including anaphylaxis, have been described with other products based on F(ab')2 of equine origin, thus there is the possibility of such reactions occurring after administration of INM005. Patients who have received prior treatment with an antivenin/antitoxin derived from equines or who have a history of hypersensitivity to such animals are at increased risk of developing severe hypersensitivity reactions to the administration of INM005 (89). The existence of any of the aforementioned history will be an exclusion criterion for the recruitment of a subject in this phase 2/3 study. (89)

An international anaphylaxis task force has recently recommended a new clinical working definition that should be useful to clinicians in making the diagnosis, and help lay people to recognize anaphylaxis (see adapted version in Box 1) (90) (90). This definition will be provided as a guideline for investigators:

Chart 1. Clinical criteria for the diagnosis of anaphylaxis

Anaphylaxis is highly likely when any of the following three criteria is met:

1. Acute onset of a condition (minutes to several hours) involving skin, mucosa, or both (e.g. generalised hives, pruritus or flushes/blushing, swelling of the lips-tongue-bell).

   And at least one of the following:

   a. Respiratory compromise (e.g. dyspnoea, bronchospasm, stridor, hypoxia).

   b. Cardiovascular compromise (e.g. hypotension, collapse).

2. Two or more of the following, with rapid presentation after exposure to an element that constitutes a probable allergen for the patient (from minutes to several hours):

   a. Skin or mucosal involvement (e.g. generalised hives, itching, flushes/blushing, swelling).

   b. Respiratory compromise (e.g. dyspnoea, bronchospasm, stridor, hypoxia).

   c. Cardiovascular compromise (e.g. hypotension, collapse).

   d. Persistent gastrointestinal symptoms (e.g. abdominal cramps, vomiting).

3. Hypotension after exposure to an allergen known to the patient (from minutes to several hours):

   Hypotension in children is defined as a systolic blood pressure value < 70 mmHg in children 1 month to 1 year of age [< 70 mmHg + (2 x age)] in children 1 to 10 years, and ≤ 90 mmHg in children 11 to 17 years.

Adapted from: Sampson [5] (D)

Source: Muraro (90)

During this phase 2/3 clinical study, the subject will be hospitalised for a period of 48 h during the treatment period. Said hospitalisation will be monitored by a doctor and a member of the nursing staff. The administration of INM005 should be carried out in a context in which there is adequate equipment, medication, including epinephrine, and trained staff in the management of hypersensitivity, anaphylaxis and shock. Subjects will be monitored for signs and symptoms of an acute allergic reaction (e.g. urticaria, pruritus, erythema, angioedema, bronchospasm with wheezing or coughing, stridor, laryngeal oedema, hypotension, tachycardia) during infusion of INM005 and after this. In the event of an anaphylactic reaction, the administration of INM005 should be discontinued immediately and appropriate emergency medical care instituted, which will be in charge of the treating physician and will be carried out in accordance with the provisions of the emergency protocol of each institution. Subject will be cared for through appropriate life support and treatment. Medications for the emergency treatment of acute hypersensitivity reactions, such as epinephrine, should be readily available. Intramuscular epinephrine is recognised as the first-line therapy for anaphylaxis, both in hospital and out-of-hospital, and should be administered without delay after identification of the condition. Additional therapies, such as supportive volume replacement therapy, nebulised bronchodilators, antihistamines, or corticosteroids, are considered supplemental to adrenaline. If necessary, the subject will be transferred to the Intensive Care Unit. The patient will be withdrawn from the study and will be subjected to control and follow-up by the treating physician until the resolution of the event (89-101).

Delayed allergic reactions (serum sickness, e.g. fever, urticarial or maculopapular rash, myalgia, arthralgia, and lymphadenopathy) have been reported with other equine F(ab')2-based products, thus the possibility of these types of reactions also exists after administration of INM005, typically 10-21 days after infusion. Patients will be monitored for signs and symptoms of a delayed allergic reaction. In the event a delayed allergic reaction (serum sickness) is suspected, appropriate medical attention should be instituted.