STATISTICAL ANALYSIS PLAN

DRUG:	INM005
STUDY NUMBER(S):	CT-INM005-01
PROTOCOL TITLE:	A stage 2/3, adaptive, randomized, 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-CoV2 disease
SPONSOR:	Inmunova S.A. 25 de Mayo 1021 (C.P. 1650), San Martín, Buenos Aires, Argentina
MOST RECENT PROTOCOL DATE AND VERSION:	1.1 dated 28-SEP-2020
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APPROVAL FORM

Protocol title: A stage 2/3, adaptive, randomized, 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-CoV2 disease

Study No.: CT-INM005-01
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Document prepared by: Santiago Pérez Lloret

Name and title	Contact information	Signature	Date
Santiago Sanguineti, Doctor in Biological Sciences Project Director	**INMUNOVA S.A** Tel: (5411) 2033 1455 - Ext. 6059 Mobile: (54911) 4564 3625 25 de mayo 1021 -B1650HMP San Martin - Buenos Aires, Argentina ssanguineti@inmunova.com		
Mariana Colonna Biochemist Clinical Research Manager	**INMUNOVA S.A** Tel: (+5411) 20331455 - Ext. 6184 Cel (+54911) 61718697 25 de mayo 1021 -B1650HMP San Martin - Buenos Aires, Argentina mcolonna@inmunova.com		
Santiago Pérez Lloret Study Statistician	**CONICET-UBA** Tel: +54 9 11 41834429 Av. San Juan 951 (C1147AAH) CABA santiagopl@conicet.gov.ar		

CHANGES IN THE AMENDMENT 1.0

In section 1.2, the secondary endpoints were simplified and standardized, and “duration of ICU admission and MRA requirement” was added.

Exploratory endpoints were added (see points 1.3 and 7.3)

In point 3, the definition of the censored data for the analysis of the endpoints was clarified.

In point 9, it was specified that only subgroup efficacy analyzes will be performed using the responder rate during the 28 days of follow-up, to minimize the number of subgroups compared. However, it was specified that the secondary endpoints of Study 2 to 9 will be analyzed if a group of special interest is identified.

STUDY SUMMARY

Title:	**A stage 2/3, adaptive, randomized, 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-CoV2 disease.**
Clinical phase:	**2/3**
Rationale:	**The pandemic caused by the new coronavirus has generated a situation unprecedented 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 cases present mild clinical presentation, approximately 15% of patients present moderate to severe cases and 5% require critical care, with respiratory assistance and a high risk of mortality. 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 favorable 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. This study aims to study the efficacy and safety of passive immunotherapy by administering hyperimmune serum (INM005) generated from antigenic stimulation to equines. INM005 is a product biologically equivalent to the anti-shiga toxin serum that works by neutralizing the interaction of SARS-CoV-2 with its cellular receptor, this way preventing the multiplication of the virus. The safety information for the anti-shiga toxin serum indicates that it is well tolerated and that no serious adverse effects or suspensions of treatment related to safety aspects have been detected. 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 28 days after the start of treatment with the research product in individuals with moderate to severe disease requiring hospitalization.**
Target population:	**Patients with moderate or severe COVID-19 as defined by NIH, which requires hospitalization, excluding patients with assisted ventilation or hospitalization in ICU.**
Number of participants:	**242 patients / approximately 10 sites**

Study design: **Randomized, double-blind, parallel group study with adaptative 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.**

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

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

After confirmation of COVID 19 diagnosis using 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:
  - any cardiovascular disease
  - any chronic pulmonary disease
  - kidney disease
  - Diabetes
  - liver disease

o immunocompromised

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

- Classification of the patient according to the 8-point WHO scale

- Physical exam

- Vital signs

• Heart rate

• Breathing rate

• Oxygen/FiO2 saturation

• Blood pressure

• Temperature

- Laboratory and imaging

• Hematology

• 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 if more than 24 hours have elapsed

-Evaluation of COVID symptoms

- Classification of the patient according to the WHO scale

- Confirm eligibility

- Randomization

- Preparation of the infusion by the unblinded personnel

- Vital signs 15 minutes prior to infusion

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

- Obtain samples for viral load (central laboratory)

- Obtain blood samples for anti SARS-CoV2 antibodies, biomarkers and immunogenicity (central laboratory)

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

Post-treatment administration procedure:

- For PK substudy:Study samples for pharmacokinetics (5 minutes post end of infusion)

- Evaluation of hypersensitivity reactions within 15 minutes post infusion

- Evaluation of adverse events and concomitant medication

- Vital signs within 15 minutes post infusion

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

- Safety laboratory 24 hours post infusion

  • Hematology

  • Full chemical panel

– Vital signs

- Classification of the patient according to the WHO scale

- Evaluation of hypersensitivity reactions

- Evaluation of adverse events and concomitant medication

- Evaluation of COVID disease and complications

Visit 3 - Day 3 (second dose of treatment)

- Preparation of the infusion by the unblinded personnel

- Evaluation of adverse events and concomitant medication

- Classification of the patient according to the WHO scale

- Evaluation of COVID disease and complications

- Vital signs 15 minutes prior to infusion

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

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

Post-treatment administration procedure:

- For PK substudy:Study samples for pharmacokinetics (5 minutes post end of infusion)

- Evaluation of hypersensitivity reactions within 15 minutes post infusion

- Evaluation of adverse events and concomitant medication

- Vital signs within 15 minutes post infusion

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

- For PK substudy:Study samples for pharmacokinetics (24 hours post second infusion)

- Safety laboratory 24 hours post infusion

    • Hematology

    • Full chemical panel

- Vital signs

- Classification of the patient according to the WHO scale

- Evaluation of hypersensitivity reactions

- Evaluation of adverse events and concomitant medication

- Evaluation of COVID 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

- Classification of the patient according to the WHO scale

- Evaluation of COVID disease and complications

- Evaluation of hypersensitivity reactions

- Evaluation of adverse events and concomitant medication

Visit 5- Day 7 (follow-up)

- Vital signs

- Classification of the patient according to the WHO scale

- Evaluation of COVID disease and complications

- Evaluation of hypersensitivity reactions

- Evaluation of adverse events and concomitant medication

- Obtain samples for viral load

- Obtain blood samples for anti SARS-CoV2 antibodies and laboratory markers

- Only for PK substudy: Obtain blood sample for the pharmacokinetics study

Visit 6- Day 14 (follow-up)

- Vital signs

- Classification of the patient according to the WHO scale

- Evaluation of COVID disease and complications

- Evaluation of hypersensitivity reactions

- Evaluation of adverse events and concomitant medication

Visit 7- Day 21 (follow-up)

- Vital signs

- Classification of the patient according to the WHO scale

- Evaluation of COVID disease and complications

- Evaluation of hypersensitivity reactions

- Evaluation of adverse events and concomitant medication

- Obtain samples for viral load

- Obtain blood samples for anti SARS-CoV2 antibodies and laboratory markers, immunogenicity

– Safety laboratory

• Hematology

• Full chemical panel

Visit 8- Day 28 (End of study)

- Vital signs

- Classification of the patient according to the WHO scale

- Evaluation of COVID disease and complications

- Evaluation of hypersensitivity reactions

- Evaluation of adverse events and concomitant medication

- Evaluation of adverse events and concomitant medication

Eligibility criteria:

Inclusion 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 for virus detection
3. Patients with moderate or severe disease by NIH definition, which requires hospitalization.
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

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 respiratory assistance or are hospitalized in the ICU at the screening visit
4. History of anaphylaxis, prior administration of equine serum (por 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, 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 enrollment, which prevents adequate follow-up of that patient

Study drug: The INM005 treatment scheme is based on a history of INM004 (equine hyperimmune antishigatoxin serum). The maximum dose tested in Phase I of INM004 was a dose of 4 mg/kg and up to 3 doses separated by 24 hours.

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 (that is, allergic reaction, anaphylaxis and serum sickness)
Pharmacokinetic assessments	A PK substudy 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 medication must be done in case of an allergic reaction > = grade 3 and/or anaphylaxis
Standard of care/ medication	Standard of care: • Each hospital • Guidelines from the Ministry of Health of Argentina: **Treatment:** There is no specific treatment recommended for COVID-19 infection. The people infected with COVID-19 must receive care to alleviate the 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. 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

Sample size	comparison), 121 subjects will be required in each treatment group, totaling 242 participating subjects.

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ABBREVIATIONS

Abbreviation	Definition
MRA	Mechanical respiratory assistance
COVID-19	Coronavirus disease
AE	adverse event
AESI	adverse event of special interest
TEAE	treatment emergent adverse event
SAE	serious adverse event
ECG	electrocardiogram
PK	pharmacokinetics
DOFS	date of onset of first symptom
ICH	International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use
NIH	National Institute of Health
BMI	body mass index
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat group
PaCO2	partial pressure of carbon dioxide
PK	pharmacokinetics
PP	Per Protocol
PT	preferred term
SoC	System Organ Class (MedDRA dictionary)

ICU	Intensive care unit

1 DEFINITION OF ENDPOINTS

This study included patients with moderate or severe COVID-19 as defined by the US National Institutes of Health (NIH), who required hospitalization, but not assisted respiration or ICU admission at the time of inclusion. Below is a description of the endpoints of the study.

1.1 Primary

The proportion of patients that showed improvement 28 days after the administration of the first dose will be evaluated. The clinical status assessment was performed using the WHO 8-point ordinal clinical status scale [1], whose categories are:
0- No evidence of infection
1- Outpatient, with no limitation to activities
2- Outpatient, with limitation to activities
3- Hospitalized with no oxygen needed
4- Use of oxygen with mask or nasal tube
5- Non-invasive ventilation or high-flow oxygen
6- Intubation and mechanical respiratory assistance
7- Mechanical ventilation and organ support (vasopressors, ECMO [extracorporeal membrane oxygenation], RRT [renal replacement therapy])
8- Death

This variable was evaluated before the start of treatment and at 1, 2, 3, 4, 5, 7, 14, 21 and 28 days its start.

The primary endpoint will consist of the proportion of “responders” at day 28, defined as subjects who show an improvement of at least 2 categories on the WHO scale recorded before treatment, or are discharged [9, 11]. The analysis will be done at D28, but if the variability is high, partial analyzes will be made according to the variability to quantify the effect based on it, given that little is known about the disease at the date of study design. This may include subgroup analysis as mentioned in section 9.

1.2 Secondary

The secondary endpoints considered in the protocol are:

1) Concentration of INM005 product in serum at different times after administration of treatment (see "Pharmacokinetic Analysis").

2) Improvement of at least 2 categories on the WHO ordinal scale of clinical status or discharge: time to event, risk of event, and rates at 7 and 14 days from the start of treatment.

3) Improvement of at least 2 categories on the WHO ordinal scale of clinical status: time to event, risk of event and rates at 7, 14 and 28 days from the start of treatment.

4) Discharge: time to event, risk of event and rates at 7, 14 and 28 days from the start of treatment.

5) Admission to ICU: time to event, risk of event and rates at 7, 14 and 28 days from the start of treatment.

6) MRA requirement: time to event, risk of event and rates at 7, 14 and 28 days from the start of treatment.

7) Mortality: time to event, risk of event and rates at 7, 14 and 28 days from the start of treatment.

8) Admission to ICU and/or MRA requirement and/or death (composite endpoint): time to event, risk of event and rates at 7, 14 and 28 days from the start of treatment.

9) Changes in the WHO Ordinal Clinical Status Scale during the 28-day follow-up.

10) Duration of admission in ICU and MRA requirement.

11) Changes in viral load from day 1 to 7 and 21 days after starting treatment

12) Variations in the reactivity of anti-SARS-CoV2 IgG and IgM antibodies, evaluated on day 1 (pre-treatment) and after 7 and 21 days of treatment.

1.3 **Exploratory**

The following will be evaluated:

1) Variations in serum levels of biomarkers of renal function, leukocyte count parameters, total neutrophil/lymphocyte ratio, procalcitonin, Troponin T, D-dimer, ferritin, LDH, C-reactive protein or other clinically relevant markers before and after 7 and 21 days of treatment.

2) Anti-INM005 antibody levels before and after 21 days of treatment.

1.4 Safety

The incidence of adverse events related to the product under study and of adverse events of special interest during the study period will be analyzed.

2 DEFINITION OF STUDY POPULATIONS

The definitions given in the protocol do not comply with the recommendations of the ICH E9 guide "Statistical Principles for Clinical Trials" [4]. For this reason, the definitions of the study populations were reviewed and those that will be used for statistical analysis are defined below.

2.1 Modified Intent-to-treat

The modified intent-to-treat group will be made up of all subjects who have been randomized to receive INM005 and who have received at least one dose of INM005. The following subjects will be excluded from this population,

- Have not met any of the major screening criteria
- Have not received any dose of the study treatment

2.2 Per Protocol

The Per Protocol population will be made up by all the subjects in the mITT who have no major protocol deviations. The following will be considered to be protocol deviations,

- Subjects who developed any of the criteria for withdrawal during the study, but were not withdrawn.
- Subject who received 1 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.

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.

2.3 **Safety**

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.

3 DATA ALLOCATION

Subjects with protocol deviations or lost to follow-up will not be replaced.

In subjects who have received at least one dose of study medication and have been evaluated at least once after said treatment, the missing information will be imputed using the LOCF method (last observation carried forward). This procedure will be used for the primary endpoint.

The secondary endpoints 4-6 and 8, deaths, lost to follow-up and patients reaching Day 28, will be treated as censored data. In these analyzes, discharged patients will be part of the population at risk.

No imputations will be made on pharmacokinetic data, nor for viral load and antibody titers analyzes.

4 ADVERSE EVENTS AND CONCOMITANT MEDICATION

AEs will be coded by PT (Preferred Term) using the Medical Dictionary for Regulatory Activities (MedDRA) classification.

The following convention is established for the closure of adverse events in the event that the subject dies:

A) For the EA that causes death, the date of death would be set as the end of the event (AE resolution date) and Outcome = "death" (according to the eCRF)

B) For the rest of EAs that are ongoing, the Outcome = "not yet recovered" will be used (according to the eCRF). The date of resolution is not filled in.

Upon completion of the subject in the study, if the investigator detects an AE in a study subject within 30 days of the last scheduled follow-up visit and considers that the event is possibly related or related to the PMI, this event should be reported. If any AE is not resolved, these events will be followed until they are resolved or until they are no longer clinically relevant and will be documented in the CH according to the GCP even though the patient has completed the study. The events related to the PMI should be followed until resolution and reported in the CRF even if the study has finished.

Their outcome must be documented in the eCRF. If the event is "ongoing" at the time of the final visit, it must be registered as such and the Outcome "not yet recovered" or "chronicity".

Concomitant medication will be coded with the WHO-ATC dictionary.

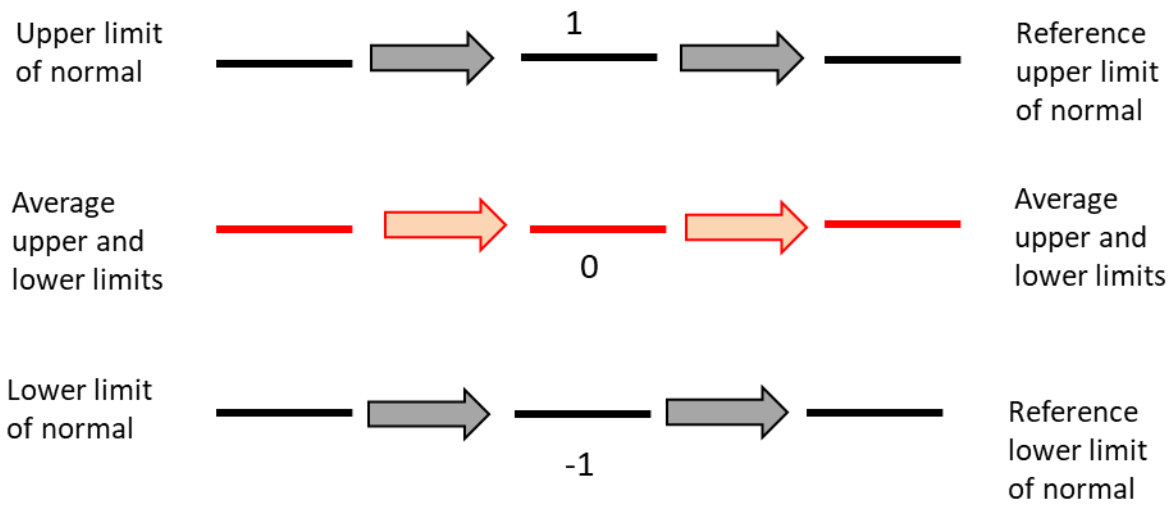
5 STANDARDIZATION OF THE LABORATORY PARAMETERS

The laboratory parameters will be re-escalated to the reference normal values provided in the following table:

Parameter	Normal range	Conventional unit
Hemoglobinemia	14-18	g/dl
Hematocrit	42-50	%
Red blood cell count	4.2-5.9	Mill/ul
Platelet count	150000-400000	/ul
White blood cell count	4000-11000	/ul
Neutrophils	2000-8500	/ul
Lymphocytes	2250-3375	/ul
Eosinophils	0-225	/ul
ASAT	0-35	IU/l
ALAT	0-35	IU/l
Alkaline phosphatase	31-150	IU/l
Total bilirubin	0.3-1.2	mg/dl
Direct bilirubin	0.0-0.3	mg/dl
Urea	8-20	mg/dl
LDH	80-225	IU/l
Creatinine	0.7-1.3	mg/dl
Albumin	3.5-5.5	g/dl
Total protein	5.5-9.0	g/dl
Blood sugar	70-99	mg/dl
Blood potassium	3.5-5.0	mEq/l
Blood sodium	136-145	mEq/l

Obtained from [10]

For this, in a first step, the results for each patient will be standardized to the normality limits of each test indicated for each patient. In a subsequent instance, the standardized values will be re-converted to medically relevant units, using the reference limits of normality. The procedure is shown graphically below:



6 INTERIM ANALYSIS

It was calculated that 121 subjects will be required for the protocol in each treatment group, with a total of 242 participating subjects (absolute effect size = 15%, power = 80%, alpha = 2.5%). An event rate under “standard of care” (placebo group) of 70% was assumed [9].

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 analyze the event rate in the group under “standard of care” (placebo) and may recommend:

1) The modification of the sample size, based on the observed event rate, or

2) The interruption of the study if:

a. It's judged that it is not feasible because it requires an excessively large sample size, or

b. It's considered futile because it has observed 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.

For the recalculation of the sample size, the following formula will be used;

$$n_A = \frac{\left(Z_{1-\alpha/2}\sqrt{2\bar{\pi}(1-\bar{\pi})} + Z_{1-\beta}\sqrt{\pi_A(1-\pi_A)+\pi_B(1-\pi_B)}\right)^2}{(\pi_A-\pi_B)^2} \quad [2]$$

7 STATISTICAL ANALYSIS OF THE RESULTS

The statistical analysis will be carried out using the "R" software (Version 4.0.1) [3], following the principles of the ICH E9 guide [4].

Comparisons of the characteristics of the subjects and other data collected pre-randomization will be performed using a t-test or a χ2 test (or their non-parametric alternatives if the assumptions are not met) [5]. A critical value of alpha of 0.05 will be used.

7.1 Primary endpoint

The proportion of "responding" subjects will be compared using a one-tailed Z test with the corresponding continuity correction [5]. It will be established that:

H0= $p_{placebo} = p_{INM005}$

H1= $p_{placebo} < p_{INM005}$

A critical value of alpha of 0.025 will be used. This will allow the assessment of the superiority of the active treatment.

7.2 Secondary endpoints

The pharmacokinetic analyzes will be described in the corresponding section.

A Kaplan Meier [5] survival curve analysis will be used for group comparison of endpoints 2 to 8. Hazard Ratios (HR) will be calculated using the Cox Proportional Hazards Regression method [5]. The event rates on day 7, 14 and 28 will be compared from the mortality tables calculated by the Kaplan Meier method. The mean time until the event will also be calculated by the Restricted Mean Survival Time (RMST) method [15].

The length of the ICU stay and the MRA requirement will be compared using a non-parametric Mann-Whitney test.

The logarithm of the viral load will be calculated before and at 7 and 21 days after treatment. The differences between groups will be compared using a mixed effects model [5], in which the subject will be considered as a random effect and the time of evaluation as a fixed factor. Methods based on analysis of variance have been shown to be more efficient than non-parametric tests for the analysis of the results of clinical trials [6]. Post-hoc paired comparisons will be made using Tukey's method. In addition, viral load will be categorized according to international cutoff levels. Differences between treatment groups will be analyzed.

A similar procedure will be followed for the anti-SARS-CoV2 antibody reactivity assay.

Finally, for the analysis of the evaluation of the WHO ordinal scale score, an analysis by Generalized Estimation Equations (Structural Equation Modeling or GEE) will be used [8]. A cumulative logit-type link function and a working correlation matrix with a first order autoregressive structure will be used. If the model cannot adjust, a sensitivity analysis will be carried out on the Area Under the Curve of the WHO scale evolution curve between day 0 and 28, by means of a T test. If it is observed that there is no adjustment, we will proceed to analyze the differences in the scale on days 7, 14, 21 and 28. An ordinal logistic regression model will be used (a method also known as the proportional-odds cumulative model) [7]. The alpha error will be adjusted to compensate for the 4 comparisons made. The Brant test will be used to verify the assumptions of the regression model [12].

7.3 Exploratory endpoints

Serum levels of Troponin T, D-dimer, ferritin, LDH, C-reactive protein, biomarkers of kidney function, leukocyte count parameters, total neutrophil/lymphocyte and procalcitonin ratio and anti-INM005 antibody levels if they do not present normal distribution they will be subjected to a logarithmic transformation. Differences between groups will be compared by Analysis of Covariance (ANCOVA). Variables that reflect the constitution of subgroups that show clinical benefits may be included.

7.4 Safety endpoints

The incidence of adverse events related to the study product and of adverse events of special interest during the study period will be compared between the groups using a χ2 test (or Fisher if the assumptions are not met) [5]. The same technique will be used for the comparison between groups of the proportion of events by SoC (MedDRA dictionary), of patients with AE, AESI, TEAE or SAE and of patients with AE observed in at least 5% of the population.

Laboratory parameters and vital signs that do not show normal distribution will be subjected to a logarithmic transformation. The differences between groups will be compared using a mixed effects model [5], in which the subject will be considered as a random effect and the time of evaluation as a fixed factor. Post-hoc paired comparisons will be made using Tukey's method. Analysis may be included in the different subgroups of clinical interest

Finally, the proportion of clinically significant abnormal findings in laboratory parameters and vital signs between treatment groups will be compared using a χ2 (or Fisher) test [5].

8 SENSITIVITY ANALYSIS

8.1 Analysis in the Per Protocol population

The analyzes mentioned in section 7.1 will be repeated in the Per Protocol population.

8.2 Effect of the research site

The absence of research site effect on the result of the primary endpoint analysis in the mITT population will be verified using a Cochran-Mantel-Haenszel analysis [5]. If a research site effect is found, additional exploratory analyzes will be conducted to better understand the effect and how it might have affected the efficacy evaluation.

8.3 Adjustment for subject baseline characteristics

If statistically significant differences were detected between the groups in their characteristics or in the variables recorded pre-randomization (considering a critical value of alpha = 0.10) or if these differences were considered clinically relevant, a multivariate

analysis of the primary endpoint will be carried out in the mITT population considering these differences. For this, a logistic regression model [5] will be used, using the treatment group and the confounding variables in a model.

8.4 Method of allocation

The analysis of the variable of primary interest (section 7.1) will be repeated in the mITT population but using a logistic regression imputation technique [5] using the characteristics of the subjects registered at the baseline visit to predict the most likely outcome at the end of the follow-up. Data will be included for all subjects for whom the primary endpoint has been recorded. The following variables will be included:

A. sex;

B. age;

C. body mass index (categorized under low weight, normal weight, overweight, obesity and morbid obesity)

D. Presence of concomitant cardiovascular, chronic pulmonary, kidney, diabetes, liver, immunocompromised, disabling neurological and other diseases,

E. severity of COVID-19 disease according to NIH classification,

F. date of onset of the first symptom to the start of treatment (DOFS),

G. reactivity of anti SARS-CoV2 IgG antibodies

The regression equation will then be used to calculate the probability of developing the event considered by the primary endpoint. If it is> 50%, it will be considered that the subject developed it.

9 EXPLORATORY SUBGROUP ANALYSIS

Patient subgroup analyzes will be conducted to explore efficacy. The mITT population will be used.

The following subgroups will be analyzed:

A. Age (categorical: <65, 65-79 years; by decade; numerical)

B. Sex

C. Race

D. Time from onset of first symptoms until start of treatment (continuous; categorical)

E. Severity of COVID-19 according to the NIH scale according to definition in clinical protocol

F. Antibody reactivity (categorical: reactive vs non-reactive; by reactivity categories [no, low, high]; numerical)

G.

H. Comorbidities (immunosuppression, diabetes, high blood pressure, cardiovascular disease, lung disease, or any)

I. Body Mass Index (categorical: normal weight, overweight, obesity and morbid obesity; numerical)

J. WHO Ordinal Scale at baseline (categorical)

K. Interactions between the items described above.

The variable that will be used for these analyzes will be the rate of responders. Survival curves will be calculated using the Kaplan Meier technique and a Cox proportional hazards model will be used to calculate the Hazard Ratio for the interaction between the treatment group and each of the variables. If differences of interest are found, differences between subgroups in secondary endpoints 2 to 13 can be analyzed.

In addition, the change in the logarithm of viral load before and after treatment will be correlated with the anti-SARS-COV2 IgG antibody titers using the Pearson parametric technique.

10 PHARMACOKINETIC ANALYSIS

This substudy was conducted in only 3 research sites. Participation in it was optional for the patient. 20 subjects were selected. Only a fraction of these subjects received the equine serum. The number of subjects can only be determined at the time of unblinding. Subjects who received placebo will not be assessed.

Samples were obtained for PK assessments immediately before the 1st administration of the study drug, at the end of the 1st administration of the study drug, 24 hours after 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, 24 hours after 2nd study drug administration and 7 days after 1st study drug administration.

For pharmacokinetic analysis, plasma concentrations will be logarithmically transformed. A mixed effects model [5] will be used to model the pharmacokinetic characteristics of the serum. The time of measurement will be included as a fixed effect and the subject as a random effect. The sex and weight of the subjects will be included as covariates.

In addition, correlations will be established between the maximum concentration of INM005 (Cmax), efficacy parameters and viral load using the Pearson method.

11 ROLES AND TIMELINES

The statistical analysis will begin after the database lock has been performed and documented. This locking will be carried out after having carried out an analysis of the protocol deviations and an initial review of the consistency of the information.

The statistical analysis will be in charge of the study statistician and will follow the plan set forth in this document. Analysis not contemplated in this plan will not be carried out.

The analysis report will be available for review 30 calendar days after the closure of the database. The review of this document will be the responsibility of the sponsor.

12 LIST OF TABLES AND FIGURES

12.1 List of Tables

No.	Title	Population	Variables included
1	Baseline characteristics of the subjects randomized to Q or R	mITT	Age, sex, ethnicity, weight, height, BMI, comorbidities, physical examination, COVID-19 symptoms, DOFS, NIH classification, WHO scale, laboratory parameters, ECG abnormalities and vital signs
2	Major protocol deviations in Q and R	mITT	Frequencies

No.	Title	Population	Variables included
3,4	Primary and secondary endpoints in Q and R	mITT and PP (primary criterion)	Patient frequency or means of survival according to Kaplan-Meier analysis
5,6	WHO ordinal scale per visit in groups Q and R	mITT	Patient frequency in each category in Days 0, 7, 14 and 28.
7			
8	Clinically significant abnormal findings in laboratory parameters in Q and R	Safety	Frequency of findings
9	Concomitant medication per group	Safety	Frequency by therapeutic groups and most frequent medications and medications of special interest
10	Adverse events per patient in groups Q and R	Safety	Number of patients with AE, TEAE, SAE, AESI and events by SOC
11	AESI in groups Q and R	Safety	Frequency of specific AESI
12	SAEs in groups Q and R	Safety	Frequency of specific SAEs, separated by fatal and non-fatal
13	Most frequent AE in groups Q and R	Safety	Frequency of specific AE observed in at least 5% of the sample
14	Events of disease progression in Q and R	Safety	Frequency of specific events

Tables will also be added to show the results of the exploratory analyzes as needed.

12.2 List of figures

No.	Title	Population	Description
1	Participant flow	mITT	No. of patients screened, randomized to each group, included in the mITT population, with protocol deviations, included in the PP population
2,3	Evolution of the WHO ordinal scale in Q and R	mITT	WHO scale
4	Primary and secondary endpoints in Q and R (survival curves)	mITT	Survival curves calculated by Kaplan-Meier
5	Evolution of SARS-CoV2 antibodies titers in Q and R	mITT	Antibody titers
6	Evolution of serum levels of Troponin T, D-dimer, ferritin, LDH, C-reactive protein	mITT	Serum levels of markers
7	Diagram of effects (forest plot) of the exploratory efficacy analysis by subgroups	mITT	Variables “A” to “I” (section 9)
8	Concentration-time curves of equine serum	PK substudy	F(ab’)2 in ng/ml over time (hours)
9	Vital signs	Safety	Vital signs values per visit
10	Laboratory parameters	Safety	Laboratory parameters values per visit

Figures will also be added to show the results of the exploratory analyzes as needed.

13 REFERENCES

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