

 <p>I.R.C.C.S. Ospedale San Raffaele</p>	<h1>Clinical Research Protocol</h1>	<p>CTC Template no. 001 Template: version no. 1 Version date: 21/04/2020</p>
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<p>Clinical trial title</p>	<p>Randomized, controlled, open label, phase 2 clinical trial of Interferon-β-1a (IFNβ-1a) in COVID-19 patients.</p>
<p>Clinical trial acronym</p>	<p>INTERCOP</p>
<p>EudraCT number</p>	<p>2020-002458-25</p>

<p>Current edition number</p>	<p>0</p>	<p>Edition date</p>	<p>14/05/2020</p>
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Signature:

Herewith I confirm that I read the study protocol carefully and declare my consent with it. I will treat and examine the patients in accordance with the study protocol, the national applicable laws, the international guidelines on good clinical practice (ICH-GCP) and the Declaration of Helsinki.

Promoter name: **Emanuele Bosi**

Date: **14 May 2020**

Promoter signature:



Protocol history

Rev.	Description of the revisions	Date
D001	Draft	21/04/2020
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2 Synopsis

2.1 General Information

Title (Acronym)	Randomized, controlled, open label, phase 2 clinical trial of Interferon- β -1a (IFN β -1a) in COVID-19 patients (INTERCOP).
Promoter	Emanuele Bosi, Professor, MD Department of Medicine IRCCS San Raffaele Hospital, Milan, Italy bosi.emanuele@hsr.it
Principal Investigator	Emanuele Bosi, Professor, MD Department of Medicine IRCCS San Raffaele Hospital, Milan, Italy bosi.emanuele@hsr.it
Objectives	
Primary Objective	To determine the efficacy of IFN β -1a as time to negative conversion of SARS-Cov-2 nasopharyngeal swab in hospitalized COVID-19 patients.
Secondary Objectives	<ul style="list-style-type: none"> I) To determine the efficacy of IFNβ-1a to improve the clinical status and respiratory functions of hospitalized COVID-19 patients. II) To determine the efficacy of IFNβ-1a to reduce mortality in COVID-19 patients. III) To determine the efficacy of IFNβ-1a to improve the chest CT scan picture in hospitalized COVID-19 patients. IV) To determine the efficacy of IFNβ-1a to reduce the time of hospitalization in hospitalized COVID-19 patients. V) To determine the efficacy of IFNβ-1a to reduce the viral load of SARS-CoV-2 measured on plasma. VI) To determine the safety of IFNβ-1a administration in hospitalized COVID-19 patients.
Exploratory objectives	<ul style="list-style-type: none"> I) To determine the efficacy of IFNβ-1a to reduce systemic inflammation in COVID-19 patients II) To determine the effect of IFNβ-1a on the transcription of interferon stimulated genes (ISG) III) To determine the influence of IFNβ-1a on the establishment of an antibody response against SARS-CoV-2 IV) To determine whether antibodies against IFNβ-1a are produced during treatment.

End points

Primary End-point

Time to negative conversion of SARS-CoV-2 nasopharyngeal swab. Viral load will be measured by RT-PCR. [Time frame: baseline, days 3, 5, 7, 9, 11, 13, 15, 21, 29]

Secondary End-points

- I)
 - a. Improvement in clinical severity score, defined as percentage of patients reporting each severity rating on a 7-point ordinal scale (see below).
[Time frame: baseline, days 7, 15, 21, 29].
 - b. Improvement in clinical severity score, defined as the time to clinical improvement of two points from the time of randomization on a 7-category ordinal scale or live discharge from the hospital, whichever comes first.
[Time frame: from baseline to day 29].
The 7-category ordinal scale consists of the following: 1) not hospitalized, with resumption of normal activities; 2) not hospitalized, but unable to resume normal activities; 3) hospitalized, not requiring supplemental oxygen; 4) hospitalized, requiring supplemental oxygen; 5) hospitalized, requiring high-flow oxygen therapy, non-invasive mechanical ventilation, or both; 6) hospitalized, requiring ECMO, invasive mechanical ventilation, or both; and 7) death.
 - c. Incidence of new oxygen use, non-invasive ventilation, or high flow oxygen devices during the trial.
[Time frame: from baseline to day 29].
 - d. Oxygenation free days in the first 28 days.
[Time Frame: from baseline to day 29].
 - e. Ventilator free days in the first 28 days.
[Time frame: from baseline to day 29].
 - f. Incidence of new mechanical ventilation use during the trial.
[Time frame: from baseline to day 29].
 - g. Number of patients transferred to Intensive Care Unit (ICU).
[Time frame: from baseline to day 29].
- II) Mortality rate.
[Time frame: from baseline to day 29].
- III) Changes from baseline in pulmonary TC imaging severity score measured with artificial intelligence and expressed as cc and percent values of diseased lung (lung consolidation, ground glass opacities and disease free)

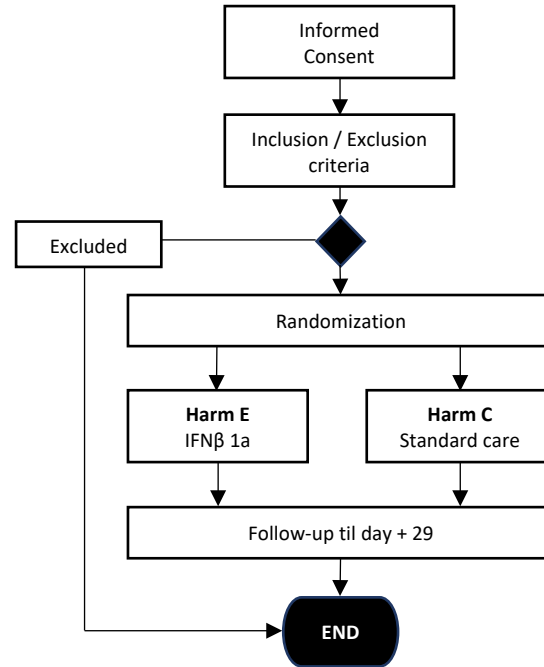
Exploratory endpoints

- [Time frame: baseline, day 21; extra follow up at 90 days]
- IV) Duration of hospital stay expressed in days.
[Time frame: from baseline to day 29].
- V) Viral load measured on plasma with RT-PCR.
[Time frame: baseline, days 3, 5, 7, 9, 11, 13, 15, 21, 29]
- VI)
- a. Number of Serious adverse events (SAE) and Adverse Drug Reaction (expected and un-expected) until the discharge from the clinical unit (discharge for any motivation).
[Time frame: from baseline to day 29].
 - b. Changes from baseline in: white blood cell count (WBC), hemoglobin, platelets, C-reactive protein (CRP), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, prothrombin time, international normalized ratio (INR), D-dimer, electrolytes (sodium, potassium, calcium), glucose.
[Time frame: baseline, days 7, 15, e 29].
- I)
- a. Cytokine and inflammatory profile (IL-6, ferritin, procalcitonin).
[Time frame: baseline, days 7, 15, 29].
 - b. White blood cell count (WBC), hemoglobin, platelets, CRP, LDH, prothrombin time, INR, D-dimer, glucose.
[Time frame: baseline, days 7, 15, 29].
- II) Plasma and peripheral blood mononuclear cell mRNA expression profile of interferon stimulated genes (ISG).
[Time frame: baseline, day 15].
- III) Antibodies to SARS-CoV-2 measured with a newly developed luciferase immunoprecipitation system (LIPS) assay, measuring IgA, IgM and IgG against RBD (receptor-binding domain RBD) and S (spike) proteins.
[Time frame: baseline, days 7, 15, 29].
- IV) Antibodies to IFN- β 1a measured by a LIPS assay.
[Time frame: baseline, days 7, 15, 29]

Criteria	
Assessment of safety	Adverse Events collection, New mechanical ventilation uses, New oxygen uses or new non-invasive ventilation or new high flow oxygen devices, number of transfers to intensive care units, WBC, haemoglobin, platelets, CRP, LDH, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Total bilirubin, creatinine, International normalized ratio (INR), D-dimer, Prothrombin time, Blood electrolytes (Na, Ca, K).
Assessment of efficacy	Time to negative conversion of nasal swabs to SARS-CoV-2, Clinical severity score, mortality, CT lung disease score, hospital stay, Transfer to Intensive Care Unit (ICU), mortality, Oxygenation free days, Ventilator free days, duration of hospital stay.
Protocol design	This is an interventional, monocentric, phase 2, randomized, open label, controlled clinical study
Experimental drug description	IFN β 1a will be administered <i>subcutaneous</i> at a dose of 44 mcg (12 million international units), administered as described in table 2. All patients will receive a total dose of 264 mcg (72 million international units) under the physician control, no dose adjustments are scheduled for the single patient.
Inclusion criteria	<ol style="list-style-type: none"> Signed informed consent; Patients hospitalized with confirmed swab RT-PCR detection of SARS-CoV-2; X-ray and/or TC diagnosed pneumonia; Age \geq18 years; Clinical status defined as 3, 4 or 5 on the aforementioned 7-point ordinal scale.
Exclusion criteria	<ol style="list-style-type: none"> Known allergy or hypersensitivity to IFNβ-1a or IFNβ-1b; Presence of severe concomitant illnesses/medical conditions that in the physician opinion do not allow participation to the study; Pregnant or lactating females; History of major depression disorder or suicidal attempt or suicidal ideation; Spontaneous blood ALT/AST levels > 5 times the upper limit of normal; Clinical status defined as 1, 2, or 6 on the aforementioned 7-point ordinal scale.
Sample size	The study is powered to assess the primary endpoint, which is time to negative conversion of the nasal swab for SARS-CoV-2. Based on the recent paper by Hung (8) and assuming a median time to negative conversion of the nasal swab for SARS-CoV-2 of 12 days in the standard of care group and 7 days in the IFN β -1a group, to detect an HR of 0.58, with a power of 80% at 5%

	<p>significance level, with an accrual duration of 6 months and a follow up of 29 days, 120 total patients need to be randomized in 2:1 ratio. With a drop out of 5%, 126 patients will be accrued: 84 patients in the IFNβ-1a arm and 42 in the standard of care arm.</p>
<p>Accrual/duration timeline</p>	<p>Anticipated start of recruitment: June 2020 Anticipated stop of recruitment: at the time of 126 enrolled patients (120 of whom to be randomized, 80 in the experimental group and 40 in the control group) End of total follow-up: 29 days after the treatment of the last patient included Draft statistical report: within 3 months from the end of total follow-up Integrated final report: within 6 months from the end of follow-up</p>
<p>Statistical design</p>	<p>The primary efficacy analysis will be done on an intent to treat basis (ITT) and will include all randomized patient. Survival analysis will be performed to address the primary endpoint of the study. Time to event is defined as the time from randomization until date of negative conversion. The date of the event (time of negative conversion) is the date of the first negative nasal swab test. Survival curves will be estimated using the Kaplan-Meier method and the Log rank test will be used to compare the outcomes of the different treatment arms. Hazard ratios will be estimated using the Cox proportional hazards model and these will be presented together with 95% two-sided confidence intervals.</p> <p>Endpoints that are measured as time from randomization will be compared between treatment groups using the Log-Rank test. Student's t-test or Mann Whitney test (depending on the data distribution pattern) will be used for inter-group comparison of continuous variables; chi-square test or Fisher exact test will be used for inter-group comparison of categorical variables.</p>

2.2 Trial Flow-chart



2.3 Treatment Schedule

Experimental drug	Dosage	Route	Day
IFNβ 1a	44 mcg	<i>subcutaneous</i>	+1
IFNβ 1a	44 mcg	<i>subcutaneous</i>	+3
IFNβ 1a	44 mcg	<i>subcutaneous</i>	+6
IFNβ 1a	44 mcg	<i>subcutaneous</i>	+9
IFNβ 1a	44 mcg	<i>subcutaneous</i>	+11
IFNβ 1a	44 mcg	<i>subcutaneous</i>	+13

2.4 Assessment Schedule

Criterium	Time >	Screening	Baseline	Treatment	FU	FU	FU	FU	FU	FU	FU	FU	FU	EXTRA FOLLOW-UP +90	
					+3	+5	+7	+9	+11	+13	+15	+21	+29		
Informed Consent		X		See table no. 3 – Treatment schedule											
Past medical history (including allergy or hypersensitivity to IFNβ-1a or IFNβ-1b, major depression disorder or suicidal attempt or suicidal ideation)		X													
Previous treatments		X													
Pneumonia (diagnosed by X-ray or TC)		X											X (TC)		X (TC)
Pregnancy or lactating		X													
Platelets, Hb, WBC			X					X			X			X	
AST, ALT		X						X			X			X	
Creatinine, Total Bilirubin			X					X			X			X	
INR, PT			X					X			X			X	
Na, Ca, K			X					X			X			X	
IL-6, ferritin, procalcitonin			X					X			X			X	
LDH			X					X			X			X	
CRP			X					X			X			X	
D-dimer			X					X			X			X	
Nasal swab for SARS-CoV-2 (diagnosis)		X													
Nasal swab for SARS-CoV-2 (quantification of viral load)			X			X	X	X	X	X	X	X	X	X	
Viral load measured on plasma			X			X	X	X	X	X	X	X	X	X	
Interferon stimulated genes analysis			X								X				
LIPS assay			X				X				X			X	
Anti-IFNβ 1a antibodies			X				X				X			X	
Clinical severity score (*to be reported every day)			X*			X*	X*	X*	X*	X*	X*	X*	X*	X*	
Transfers to Intensive Care Unit (ICU)							X				X	X		X	
Adverse Events collection							X				X			X	
Oxygen-free days							X				X			X	
New oxygen or non-invasive ventilation support uses							X				X			X	
New mechanical ventilation uses							X				X			X	
Ventilator-free days							X				X			X	

3 Acronyms

ADR	Adverse Drug Reaction
AE	Adverse Event
COVID-19	Coronavirus Disease
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
ECMO	Extracorporeal membrane oxygenation
IEC	Independent Ethical Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-6	Interleukin 6
ICU	Intensive Care Unit
IFN β -1a	Interferon- β -1a
LIPS	Luciferase immunoprecipitation system
mRNA	Messenger RNA
RBD	Receptor-binding domain
RT-PCR	Real Time PCR
SARS-Cov-2	Severe Respiratory Illness Coronavirus 2
SAE	Serious adverse events
SUSAR	Suspected unexpected serious adverse reaction

4 Background

Interferon beta (IFN β) is a cytokine belonging to a group of naturally occurring proteins, which interact with cell surface molecules ensuing in intracellular antiviral, anti-proliferative, and immuno-modulatory effects.

As a therapeutic agent, IFN β is a recombinant protein currently approved for the treatment of multiple sclerosis in two therapeutic formulations: IFN β -1a and IFN β -1b. In addition to its broad-range immunomodulatory effects, IFN β has direct antiviral activity.

Previous investigation in severe acute respiratory syndrome coronavirus (SARS-CoV) (1) and Middle East Respiratory Syndrome coronavirus (MERS-CoV) (2) indicated that IFN β might be a valid candidate to treat COVID-19.

While there are no clinical trials in SARS, a study testing IFN β -1b in MERS patients is currently ongoing and results are expected by December 2020 (MIRACLE trial, NCT00419562).

In a mouse model of MERS, IFN β -1b ameliorated the pulmonary function of infected mice when administered in therapeutic settings at a dose mirroring that currently used in the MIRACLE trial, although no changes in signs of acute lung injury were observed (3). Moreover, IFN β -1b was also efficacious in a nonhuman primate common marmoset model of MERS (4).

A recent study of SARS-CoV-2 infection has reported that type III and type-I interferons, of which IFN β is a member, are downregulated both in SARS-CoV-2 infected cells and in the lung tissue of patients deceased with COVID-19 (5), suggesting a pathogenic mechanism similar to that of SARS-CoV and MERS-CoV (6).

The unprecedented emergency of the COVID-19 pandemic, with no available drugs of proven efficacy, provided a compelling reason to repurpose drugs already marketed with other indications for treating SARS-CoV-2 infection. Among these, IFN β looked immediately attractive and some clinical trials were started, including the World Health Organization (WHO) sponsored SOLIDARITY trial program, in which IFN β is being tested in combination with lopinavir/ritonavir (7). Furthermore, most recently an open label, randomized trial showed that IFN β -1b in addition to lopinavir-ritonavir and ribavirin was superior to lopinavir-ritonavir alone in shortening the time to negative conversion of nasal swabs for SARS-CoV-2, alleviating symptoms and reducing the duration of hospital stay (8). The findings of this study indicate the urgent need of trials specifically addressed to test IFN β efficacy in COVID-19 patients.

5 Rationale

The purpose of this clinical trial is to test the efficacy of one of the two available formulations of IFN- β , Interferon- β -1a (IFN β -1a), in COVID-19 patients in an open label, randomized clinical trial. Since two clinical stages of COVID-19 are emerging, an early one with typical clinical characteristics of a viral infection (fever, malaise, cough) and a later one with pneumonia leading to progressive respiratory failure, associated with heavy, cytokine-mediated, inflammation, an intervention by a compound possessing both antiviral activity and immunomodulatory effects would be most effective at the earliest possible stage. In that perspective, patients identified as suitable for the enrolment are those symptomatic at the time of diagnosis, with mild-to-moderate radiologic signs of pneumonia and no Acute Respiratory Distress Syndrome (ARDS). Nonetheless, IFN β -1a is likely to be safe also in the case of progression to ARDS, as shown in a recent trial (9).

The design of the study is to test IFN β -1a in addition to standard of care compared with standard of care alone. Due to current unavailability of pharmacological compounds of proven efficacy against SARS-Cov-2, the standard of care for COVID-19 patients at the San Raffaele Hospital includes any pharmacological (e.g. antibiotics, etc.) and non-pharmacological (e.g. oxygen, ventilation, etc.) treatments prescribed on clinical grounds, with no other drugs addressed against the etiologic agent SARS-Cov-2.

6 Objectives

6.1 Primary Objective

To determine the efficacy of IFN β -1a as time to negative conversion of SARS-Cov-2 nasopharyngeal swap in hospitalized COVID-19 patients.

6.2 Secondary Objectives

- I) To determine the efficacy of IFN β -1a to improve the clinical status and respiratory functions of hospitalized COVID-19 patients.
- II) To determine the efficacy of IFN β -1a to reduce mortality in COVID-19 patients
- III) To determine the efficacy of IFN β -1a to improve the chest CT scan picture in hospitalized COVID-19 patients.
- IV) To determine the efficacy of IFN β -1a to reduce the time of hospitalization in hospitalized COVID-19 patients.
- V) To determine the efficacy of IFN β -1a to reduce the viral load of SARS-CoV-2 measured on plasma
- VI) To determine the safety of IFN β -1a administration in hospitalized COVID-19 patients.

6.3 Exploratory Objectives

- I) To determine the efficacy of IFN β -1a to reduce systemic inflammation in COVID-19 patients
- II) To determine the effect of IFN β -1a on the transcription of interferon stimulated genes (ISG)
- III) To determine the influence of IFN β -1a on the establishment of an antibody response against SARS-CoV-2
- IV) To determine whether antibodies against IFN β -1a are produced during treatment

7 End-points

7.1 Primary End-point

Time to negative conversion of SARS-CoV-2 nasopharyngeal swab. Viral load will be measured by RT-PCR. [Time frame: baseline, days 3, 5, 7, 9, 11, 13, 15, 21, 29]

7.2 Secondary End-points

- I)
 - a. Improvement in clinical severity score, defined as percentage of patients reporting each severity rating on a 7-point ordinal scale (see below). [Time frame: baseline, days 7, 15, 21, 29].
 - b. Improvement in clinical severity score, defined as the time to clinical improvement of two points from the time of randomization on a 7-category ordinal scale or live discharge from the hospital, whichever comes first. [Time frame: from baseline to day 29]. *The 7-category ordinal scale consists of the following: 1) not hospitalized, with resumption of normal activities; 2) not hospitalized, but unable to resume normal activities; 3) hospitalized, not requiring supplemental oxygen; 4) hospitalized, requiring supplemental oxygen; 5) hospitalized, requiring high-flow oxygen therapy, non-invasive mechanical ventilation, or both; 6) hospitalized, requiring ECMO, invasive mechanical ventilation, or both; and 7) death.*
 - c. Incidence of new oxygen use, non-invasive ventilation, or high flow oxygen devices during the trial. [Time frame: from baseline to day 29].
 - d. Oxygenation free days in the first 28 days. [Time Frame: from baseline to day 29].
 - e. Ventilator free days in the first 28 days. [Time frame: from baseline to day 29].
 - f. Incidence of new mechanical ventilation use during the trial. [Time frame: from baseline to day 29].
 - g. Number of patients transferred to Intensive Care Unit (ICU). [Time frame: from baseline to day 29].
- II) Mortality rate. [Time frame: from baseline to day 29].
- III) Changes from baseline in pulmonary TC imaging severity score measured with artificial intelligence and expressed as cc and percent values of diseased lung (lung consolidation, ground glass opacities and disease free) [Time frame: baseline, day 21; extra follow up at 90 days].
- IV) Duration of hospital stay expressed in days. [Time frame: from baseline to day 29].
- V) Viral load measured on plasma with RT-PCR. [Time frame: baseline, days 3, 5, 7, 9, 11, 13, 15, 21, 29].
- VI)
 - a. Number of Serious adverse events (SAE) and Adverse Drug Reaction (expected and unexpected) until the discharge from the clinical unit (discharge for any motivation). [Time frame: from baseline to day 29].

- b. Changes from baseline in: white blood cell count (WBC), hemoglobin, platelets, C-reactive protein (CRP), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, prothrombin time, international normalized ratio (INR), D-dimer, electrolytes (sodium, potassium, calcium), glucose. [Time frame: baseline, days 7, 15, e 29].

7.3 Exploratory End-points

- I)
 - a. Cytokine and inflammatory profile (IL-6, ferritin, procalcitonin). [Time frame: baseline, days 7, 15, 29].
 - b. White blood cell count (WBC), haemoglobin, platelets, CRP, LDH, prothrombin time, INR, D-dimer, glucose. [Time frame: baseline, days 7, 15, 29].
- II) Plasma and peripheral blood mononuclear cell mRNA expression profile of interferon stimulated genes (ISG). [Time frame: baseline, day 15].
- III) Antibodies to SARS-CoV-2 measured with a newly developed luciferase immunoprecipitation system (LIPS) assay, measuring IgA, IgM and IgG against RBD (receptor-binding domain RBD) and S (spike) proteins [Time frame: baseline, days 7, 15, 29].
- IV) Antibodies to IFN- β 1a measured by a LIPS assay [Time frame: baseline, days 7, 15, 29].

8 Criteria

8.1 Safety criteria

8.1.1 Safety profile IFNβ-1a

The safety profile of single-agent IFNβ 1 is based on Rebif® Summary of Product Characteristic 2010 using the MedDRA (Medical Dictionary for Regulatory Activities) terms, reported below:

<i>System Organ Class</i>	<i>Very Common ADR</i> <i>frequency of occurrence ≥1/10</i>	<i>Common ADR</i> <i>frequency of occurrence</i> <i>≥1/100 to 1/10</i>
General disorders and administration site conditions	Injection site inflammation, injection site reaction, influenza-like symptoms	Injection site pain, fatigue, rigors, fever
Investigations	Asymptomatic transaminase increase	Severe elevation of transaminase
Blood and lymphatic system disorders	Neutropenia, lymphopenia, leucopenia, thrombocytopenia, anemia	
Psychiatric disorders		Depression, insomnia
Nervous system disorders	Headache	
Gastrointestinal disorders		Diarrhea, vomiting, nausea
Skin and subcutaneous tissue disorders		Pruritus, rash, erythematous rash, maculo-papular rash
Musculoskeletal and connective tissue disorders		Myalgia, arthralgia

Table 3a – Summary of the Most Frequent IFNβ 1a (Rebif®) Adverse Reactions by MedDRA System Organ Class

8.1.2 Adverse Event (AE)

An adverse event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

8.1.2.1 Documentation of (serious) AE

Between day 1 and day 29 the patient will be asked and examined by the investigator for the occurrence of AEs. This time period is assumed to be appropriate for the evaluation of adverse

events directly related to the conditioning regimen. All AEs will be documented using CTCAE v3.0 terms (see Appendix), including

- Severity (listed under)
- Onset date
- End date
- Causality assessment with experimental drug
- Action taken
- Outcome

The severity of AEs is defined as (see also CTCAE v3.0):

- Grade 1 mild
- Grade 2 moderate
- Grade 3 severe
- Grade 4 life-threatening
- Grade 5 death

All clearly related signs, symptoms and abnormal diagnostic procedures should be grouped together and recorded as a single term in the CRF.

8.1.2.2 Forwarding:

Fax the SAE/SUSAR module to the Ethics Committee of the San Raffaele Hospital +39 02 2643.2643

	Documentation	Report	Time
Serious (AE, ADR)	Patient's chart + CRF + SAE-Form	Investigator forwards SAE-form to I.E.C.	Within 24 h
Non-serious (AE, ADR)	Patient's chart + CRF	-	-

Table 4 – SAE/ADR timeline

8.1.3 Adverse Drug Reaction (ADR)

An Adverse reaction (ADR): all untoward and unintended responses to an investigational medicinal product related to any dose administered. The phrase responses to an investigational medicinal product means that a causal relationship between the investigational medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

8.1.3.1 Attribution Definitions

Not related: An adverse event that is not related to the use of the investigational product.

Doubtful: An AE for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible: An AE that might be due to the use of the investigational product. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable: An AE that might be due to the use of the investigational product. The relationship in time is suggestive (e.g., confirmed by de-challenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

Very likely: An AE that is listed as a possible adverse event reaction, and cannot be reasonably explained by an alternative explanation, e.g., concomitant investigational drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by de-challenge and re-challenge).

8.1.4 Serious adverse event (SAE) or Serious Adverse Reaction (Serious ADR)

SAE or SAR: any untoward expected medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

8.1.5 Unexpected adverse reaction (UAR)

UAR: an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).

8.1.6 Suspected unexpected serious adverse reaction (SUSAR)

SUSAR: an adverse event assessed as serious and unexpected and for which there is a reasonable suspected causal relationship with an investigational medical product.

8.1.7 Pharmacovigilance Procedure

Serious Adverse Event: The Investigator shall report all SAE immediately to the Promoter and Ethics Committee. The Investigator must fill the SAE report no later than 15 days. For reported deaths of a subject, the Investigator shall supply the Promoter and Ethics Committee with any additional information requested.

Suspected Unexpected Serious Adverse Reaction (SUSAR): In case of a Serious ADR that is unexpected, the Investigator/Sponsor must report the reaction as soon as possible (and in any case no later than 7 days for reactions that are fatal or life-threatening, and no later than 15 days for all other SUSARs) to the competent Regulatory Authorities and to the competent Ethics Committee (and that relevant follow-up information is subsequently communicated within an additional eight days).

Periodic reporting: Once a year throughout the trial, the Investigator should provide to Competent Regulatory Authorities and the Ethics Committee an Annual Safety Report, that is, a listing of all suspected Serious ADRs, which have occurred over this period and a report of the subjects' safety.

Adverse event recording: All AEs/ADRs regardless of seriousness or relationship to Medicinal Product or expectedness are to be recorded on the corresponding page(s) included in the Case Report Form. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, maximal intensity, action taken with respect to Medicinal Product, corrective therapy given, outcome and his/her opinion as to whether there is a reasonable possibility that the event was caused by the study Medicinal Product.

The investigator shall keep detailed records of all adverse events, which are reported. These reports must be provided to the competent Authorities if they so request.

8.1.8 Follow-up of AE / SAE / ADR

The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any event (clinical signs, laboratory values or other, etc...) until the return to normal or until consolidation of patient conditions.

In the case of any **Serious Adverse Event or Serious Adverse Drug Reaction**, the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient left the study and that the Ethical Committee may request additional investigations.

8.1.9 List of safety criteria used in the trial

- Adverse Events collection
- New mechanical ventilation uses
- New oxygen uses or new non-invasive ventilation or new high flow oxygen devices.
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Total bilirubin
- International normalized ratio (INR)
- Prothrombin time
- Blood electrolytes (Na, Ca, K)
- Creatinine
- Blood white cell count
- Haemoglobin
- Platelets

8.2 List of efficacy criteria used in the trial

- Clinical severity score
- Hospitalization
- Transfer in Intensive Care Unit (ICU)
- Nasal swab for SARS-CoV-2
- Overall Survival
- Oxygenation free days
- Ventilator free days

9 Overall design

9.1 Type of study

This is an interventional, monocentric, phase 2, randomized, open label, controlled clinical study.

9.2 Randomization

9.2.1 Type of randomization

Patients will be randomized 2:1 to IFN β -1a (Group 1, active treatment) or standard of care (Group 2, control arm), using a computer-generated list of random treatment allocations which is produced prior to the study start. The permuted block randomization method will be used to randomize subjects into groups that result in equal sample sizes.

9.2.2 Randomization procedure

Participants who meet all eligibility criteria will be randomized by assigning a unique randomization number on visit 2. Details of the allocated group will be given on cards included in sequentially numbered, opaque sealed envelopes. Envelopes must be opened sequentially. To prevent subversion of the allocation sequence, the name and date of birth of the participant will

be written on the envelope. Once a randomization number has been assigned it cannot be re-assigned. The group assigned and the linked randomization code will be reported in CRF.

9.3 Blinding

9.3.1 Type of blinding

This is an open label trial.

9.4 Subject selection

9.4.1 Inclusion criteria

No.	Criterion	Answer	
01	Informed consent signed	<input type="radio"/> Yes	<input type="radio"/> No
02	Patients hospitalized with confirmed swab RT-PCR detection of SARS-CoV-2	<input type="radio"/> Yes	<input type="radio"/> No
03	X-ray and/or TC diagnosed pneumonia	<input type="radio"/> Yes	<input type="radio"/> No
04	Age \geq 18 years	<input type="radio"/> Yes	<input type="radio"/> No
05	Clinical status defined as 3, 4 or 5 on the aforementioned 7-point ordinal scale	<input type="radio"/> Yes	<input type="radio"/> No

Table 5 – Inclusion criteria

9.4.2 Exclusion criteria

No.	Criterion	Answer	
01	Known allergy or hypersensitivity to IFN β -1a or IFN β -1b	<input type="radio"/> Yes	<input type="radio"/> No
02	Presence of severe concomitant illnesses / medical conditions that in the physician opinion doesn't allow the inclusion	<input type="radio"/> Yes	<input type="radio"/> No
03	Pregnant or lactating females	<input type="radio"/> Yes	<input type="radio"/> No
04	History of major depression disorder or suicidal attempt or suicidal ideation	<input type="radio"/> Yes	<input type="radio"/> No
05	Spontaneous blood ALT/AST levels > 5 times the upper limit of normal	<input type="radio"/> Yes	<input type="radio"/> No
06	Clinical status defined as 1, 2, or 6 on the aforementioned 7-point ordinal scale	<input type="radio"/> Yes	<input type="radio"/> No

Table 6 – Exclusion criteria

9.5 Protocol schedule and timelines

Anticipated start of recruitment: June 2020

Anticipated stop of recruitment: 126 enrolled patients (120 of whom to be randomized, 80 in the experimental group and 40 in the control group respectively 80 – 40)

End of total follow-up: 29 days after the treatment of the last patient included

Draft statistical report within 3 months from the end of total follow-up

Integrated final report within 6 months from the end of follow-up

9.6 Study Procedure and Study Flow-chart

Starting from the signature of the informed consent by the patient or patient's legal tutor, the subjects is considered enrolled in the clinical trial.

A patient screening number will be assigned consecutively in increasing order starting from '001'. A screened patient identification list will be kept. After randomization a definitive number will be assigned to the subject as described below:

Subject number					
Screening number			Treatment number		
0	0	1	E (For Experimental group)		0
			C (for control group)		
					1

Seven protocol phases are foreseen:

- Screening phase, during which the conditions required by the clinical protocol for patients' inclusion/exclusion will be assessed (screened subject).
- Inclusion phase: At the end of the screening phase, the inclusion/exclusion criteria of the study will be evaluated (enrolled subject).
- Randomization process: to apply the randomization process (described previously).
- Baseline phase: carried from the end of the screening phase to the day before the start of treatment.
- Treatment phase: from day +1 to day + 13(subject treated).
- Follow-up phase: 29 days after the experimental drug administration.
- End of study phase: at the end time to discharge

Criterium	Time >	Screening	Baseline	Treatment	FU +3	FU +5	FU +7	FU +9	FU +11	FU +13	FU +15	FU +21	FU +29	EXTRA FOLLOW-UP +90	
Informed Consent		X		See table no. 3 – Treatment schedule											
Past medical history (including allergy or hypersensitivity to IFNβ-1a or IFNβ-1b, major depression disorder or suicidal attempt or suicidal ideation)		X													
Previous treatments		X													
Pneumonia (diagnosed by X-ray or TC)		X											X (TC)		X (TC)
Pregnancy or lactating		X													
Platelets, Hb, WBC			X					X				X		X	
AST, ALT		X						X				X		X	
Creatinine, Total Bilirubin			X					X				X		X	
INR, PT			X					X				X		X	
Na, Ca, K			X					X				X		X	
IL-6, ferritin, procalcitonin			X					X				X		X	
LDH			X					X				X		X	
CRP			X					X				X		X	

Table 1 – Follow-up scheme

Criterium	Time >													EXTRA FOLLOW-UP +90
	Screening	Baseline	Treatment	FU +3	FU +5	FU +7	FU +9	FU +11	FU +13	FU +15	FU +21	FU +29		
D-dimer		X				X				X		X		
Nasal swab for SARS-CoV-2 (diagnosis)	X													
Nasal swab for SARS-CoV-2 (quantification of viral load)		X		X	X	X	X	X	X	X	X	X		
Viral load measured on plasma		X		X	X	X	X	X	X	X	X	X		
Interferon stimulated genes analysis		X								X				
LIPS assay		X			X					X		X		
Anti-IFNβ 1a antibodies		X			X					X		X		
Clinical severity score (*to be reported every day)		X*		X*	X*	X*	X*	X*	X*	X*	X*	X*		
Transfers to Intensive Care Unit (ICU)					X					X	X	X		
Adverse Events collection					X					X		X		
Oxygen-free days					X					X		X		
New oxygen or non-invasive ventilation support uses					X					X		X		
New mechanical ventilation uses					X					X		X		
Ventilator-free days					X					X		X		

Table 1 – Follow-up scheme

9.6.1 Trial flow-chart

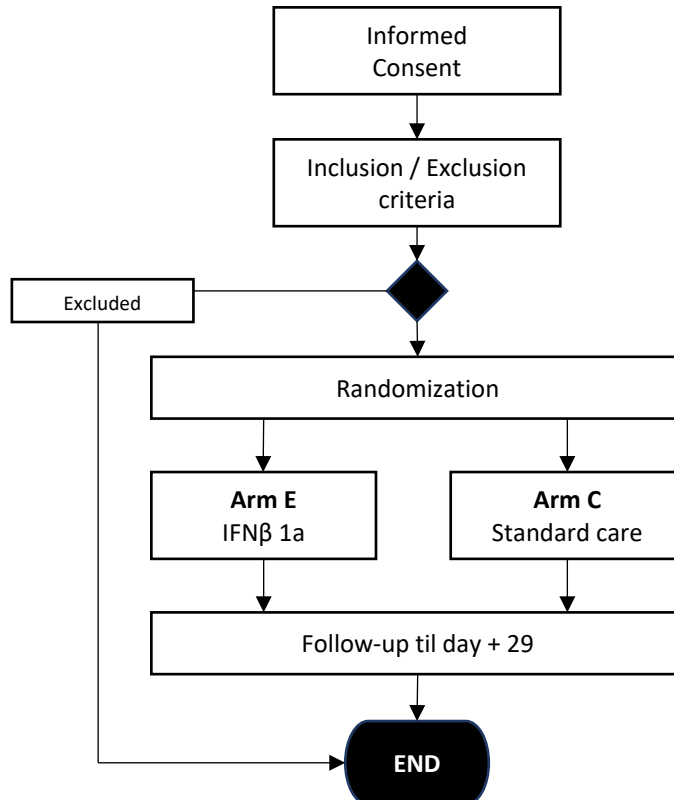


Figure 1 – Trial Flow-chart

9.6.2 End of Study

For single subject: natural termination.

The participation of the patient in the study is regularly ended:

- At the end of the follow-up.
- In case of death

For single subject: premature termination.

The patient may drop out of the clinical study at any time without stating reasons. This may not have any negative consequences for the patient's further treatment.

Possible reasons for withdrawal of the patient are:

- Withdrawal of the consent.
- Any clinical condition that in the Investigator's opinion could become dangerous for the patient and prevent the good conduction of the clinical trial.
- Protocol violation that could compromise the quality of study data.
- Lack of co-operation/compliance of the patient.
- Occurrence of new diseases that could influence the treatment efficacy, for which the study medication is contraindicated or that are treated with a medication that is not permitted as a concomitant medication.
- Lack of experimental treatment administration due to failure to release the Medicinal Product lot.
- Lost to the follow-up.

The patients may withdraw from the study, if they decide to do so, at any time and for any reason. Patients who have been withdrawn from the study cannot be re-included in the trial.

9.6.3 Follow-up procedure for withdrawn patients

All withdrawn patients should be recorded by the Investigator in the appropriate pages of the CRF when considered as confirmed. If possible, the patients should be assessed using the procedure planned for the end of study visit. If an event causing dropout corresponds to the definition of a Serious AE/ADR, the investigator carries out the pharmacovigilance procedure described. For patients considered lost to follow-up, the CRF must be filled in up to the last visit performed. The Investigator should make every effort to re-contact and to identify the reason why the patient failed to attend the visit and to determine his/her health status.

9.6.3.1 Natural study termination

At the end of total follow-up.

9.6.3.2 Premature study termination

The study can be suspended or terminated by the promoter in agreement with the Ethical Committee after:

- Reconsideration of the risk/benefit ratio (significant increase of risk/significant increase of benefit).

10 Treatment Plan

10.1 Experimental Treatment/Drug

IFN β -1a (Rebif®) will be administered *subcutaneous* at a dose of 44 mcg (equivalent to 12 million international units), administered as described in table 2. All patients will receive a total dose of 264 mcg under the physician control, no dose adjustments are scheduled for the single subject.

Experimental drug	Dosage	Route	Day
IFN β 1a	44 mcg	<i>subcutaneous</i>	+1
IFN β 1a	44 mcg	<i>subcutaneous</i>	+3
IFN β 1a	44 mcg	<i>subcutaneous</i>	+6
IFN β 1a	44 mcg	<i>subcutaneous</i>	+9
IFN β 1a	44 mcg	<i>subcutaneous</i>	+11
IFN β 1a	44 mcg	<i>subcutaneous</i>	+13

Table 2 – Treatment scheme

10.2 Identity of investigational product

<u>Investigational product:</u>	IFN β 1a
<u>Route of administration:</u>	Subcutaneous
<u>Chemical name:</u>	IFN β 1a
<u>Appearance:</u>	Transparent
<u>Solubility:</u>	Solution
<u>Stability:</u>	Not reconstituted
<u>Dosage forms:</u>	44 mcg
<u>Recommended solvent:</u>	No solvent foreseen

10.1 Experimental drug managing

The acquisition, labelling, storage, conservation, preparation, distribution and eventual disposal of the experimental drug will be managed by the centralized OSR pharmacy.

10.2 Methods of assigning patients to treatment groups

The procedure for assigning to treatment group is describing in the randomization procedure.

10.3 Blinding procedure

This is an open label study.

11 Ethical considerations

11.1 Responsibilities of the Investigator(s)

The Investigator(s) undertake(s) to perform the study in accordance with this Protocol, Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with the investigational product schedule, visits schedule and procedures required by the protocol.

The Investigator agrees to provide all information requested in the Case Report Form in an accurate and legible manner.

11.2 Independent Ethics Committees approval

The trial protocol as well as the patient information sheet, data protection declaration and informed consent form has been approved by the ethics committee.

11.3 Ethical conduct of the study

The study will be performed according the ethical principles laid down in the latest accepted version of the Declaration of Helsinki.

11.4 Patient information and informed consent

Every patient will be informed about the modalities of the clinical study in accordance with the enclosed patient information. The patient is to be informed both in writing and verbally by the investigating physician. The patient must be given ample opportunity to decide whether or not to participate in this study and to ask questions concerning this. It must also be made clear to the patient that he/she can withdraw from the study at any time without giving reasons and that he/she will not be in any way disadvantaged by this.

The points mentioned in the information sheet must be communicated to the patient in language he/she understands. The informing physician and the patient must each personally date and sign an informed consent form with a declaration on data privacy. Any informed consent will be part of the investigator's file and retained with it. The patient will retain a copy of the patient information.

11.5 Minimizing distress

This study is designed to minimize the discomfort of those enrolled, moreover, the study is designed and conducted by investigators experienced in the treatment of adult patients in critical or life-threatening conditions.

11.6 Minimizing Risk

However important a study may be to prove or disprove the value of a treatment, participants may suffer injury as a result of inclusion in the study, even if the whole community benefits. Every effort is made to anticipate and reduce known hazards.

Investigators are fully aware before the start of a clinical study of all relevant preclinical and clinical toxicity of the experimental medicinal product. To minimize risk in clinical studies, those conducting the study are properly trained and experienced in studying the population treated, including the evaluation and management of potential adverse events.

In designing studies, every attempt is made to minimize the number of participants and of procedures, consistent with good study design. Mechanisms are in place to ensure that a study can be rapidly terminated should an unexpected hazard be noted.

12 Data management

12.1 Definition of source data and source documents

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

All parameters asked for in the case report form (CRF) should be documented in the source documents (see the follow scheme).

Parameter	Source document
Medical history / patient's eligibility	- patients' charts
Adverse events	- patients' charts - laboratory reports - doctor's letters - Nurses documentation
Tests	- patients' charts
Survival	- patients' charts

Table 7 – List of parameters and its source

12.2 Documentation of data in the case report form (CRF)

All relevant data collected during the study for all of the patients enrolled in the study shall be entered in the CRF by the responsible investigator or someone authorised by him in a timely manner so that they are clear and legible. The physician shall confirm the completeness, correctness and plausibility of the data by his signature with the date. The entries shall be made with black ballpoint pen.

The properly filled in CRF will remain in the trial centre, in case of on-line web CRF a copy of all pages are conserved in the trial centre.

All the health workers, involved in the data management, have attended a specific course on use of CRF.

12.3 Data management

The data will be recorded in the CRF designed for this study. All CRF will be checked for completeness, plausibility and compliance with the ICH guidelines and the institutional SOPs.

12.4 Record keeping

The investigator shall arrange for the retention of the patient identification list, the signed informed consent forms and the signed data protection declaration for at least 15 years after the completion or discontinuation of the study. Patient files and other source data shall be kept for the maximum period of time permitted by the hospital.

The sponsor will keep essential documents according to ICH-GCP, chapter 8.

13 Statistical design

13.1 Sample size

The study is powered to assess the primary endpoint, which is time to negative conversion of the nasal swab for SARS-CoV-2. Based on the recent paper by Hung (8) and assuming a median time to negative conversion of the nasal swab for SARS-CoV-2 of 12 days in the standard of care group and 7 days in the IFN β -1a group, to detect an HR of 0.58, with a power of 80% at 5% significance level, with an accrual duration of 6 months and a follow up of 29 days, 120 total patients need to be randomized in 2:1 ratio. With a drop out of 5%, 126 patients will be accrued: 84 patients in the IFN β -1a arm and 42 in the standard of care arm.

13.2 Statistical analysis

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed.

Continuous variables will be described by mean, standard deviation, median, minimum, and maximum. Categorical variables will be described by number and percentage of subjects in each category.

The primary efficacy analysis will be done on an intent to treat basis (ITT) and will include all randomized patient. Survival analysis will be performed to address the primary endpoint of the study. Time to event is defined as the time from randomization until date of negative conversion. The date of the event (time of negative conversion) is the date of the first negative nasal swab test, confirmed by a second test performed at least 48 hours apart. Data for death patients are censored at the time of last nasal swab test.

Survival curves will be estimated using the Kaplan-Meier method and the Log rank test will be used to compare the outcomes of the different treatment arms. Hazard ratios will be estimated using the Cox proportional hazards model and these will be presented together with 95% two-sided confidence intervals

Endpoints that are measured as time from randomization will be compared between treatment groups using the Log-Rank test. Student's t-test or Mann Whitney test (depending on the data distribution pattern) will be used for inter-group comparison of continuous variables; chi-square test or Fisher exact test will be used for inter-group comparison of categorical variables.

The primary analysis set for safety analyses is defined as the Safety Analysis Set, which will include all participants who are randomized and have received at least 1 dose of study treatment. All safety data collected from the randomization date through the last follow-up visit will be summarized by treatment group.

Statistical significance will be determined at 5% significance level. Analysis will be performed by SAS software Version 9.2 or later (SAS Institute, Inc, Cary, North Carolina, United States).

14 Quality assurance and quality control

14.1 Definitions

Audit: A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Monitoring: The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Quality Assurance (QA): All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Quality Control (QC): The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

14.2 Monitoring.

A comprehensive quality control can be ordered in the form of monitoring. It might include checking the whole course of the study, the management of documentation, the management of data, the management of subject enrolled the management of experimental drug and the management of biological sample. The promoter of the study will be in charge for monitoring. The investigators will assure the monitoring of the clinical study to assure conformance to protocol as well as the completeness, correctness and plausibility of the completed case report forms (CRF).

14.3 Deviation from study protocol.

Every deviation from the trial protocol must be specified and documented separately for each patient. The investigator must consult with the monitor and discuss the type and extent of deviation as well as the possible consequences for further participation of the patient in the study. If the evaluability of a patient is questionable the coordinating investigator will be consulted.

14.4 Audits and inspections

If necessary a comprehensive quality control could be ordered in the form of an audit. It might include checking the whole course of the study, the documentation, statistical analysis and the investigators.

The promoter guarantees the availability for the inspections from the regulatory agencies.

15 Formalities/Regulatory aspects

15.1 Legal regulations and guidelines

This study will be conducted in compliance with the regulations of the latest versions of the current applicable laws: the last version of "Declaration of Helsinki" and the principles of good clinical practice (ICH-GCP).

15.2 Patient insurance

The Promoter certifies that it has taken out a liability insurance policy which covers the liability of the Investigator and his/her co-workers and which is in accordance with local laws and requirements. An abstract copy of insurance certificate will be archived in Trial Master File.

15.3 Financial aspects

The sponsor of the trial will be the IRCCS Ospedale San Raffaele. A contract between IRCCS Ospedale San Raffaele (via Olgettina, 60 – Milano) and Merck Serono S.p.A. assigned a grant to cover the costs of drug (Rebif®) supply and delivery.

15.4 Final study report

The Promoter will be responsible for preparing and submit a Final Clinical Study Report

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