EUnetHTA Joint Action 3 WP4

"Rolling Collaborative Review" of Covid-19 treatments

INTERFERON BETA-1A (IFN B-1A) AND NOVAFERON (NOVA) FOR THE TREATMENT OF COVID-19

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Monitoring Report

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Conflict of interest

All authors and co-authors involved in the production of this living document have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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LIST OF ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced therapy medicinal product
CI	Confidence Interval
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
ICD	International Classification of Diseases
IFN β-1a	Interferon beta-1a
ITT	Intention-to-treat
MD	Mean Difference
MeSH	Medical Subject Headings
n.a.	Not applicable
NR	Not reported
PP	Per Protocol
RCT	Randomized Controlled Trial
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SMD	Standardized Mean Difference
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
WP4	Work Package 4

1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

- to inform health policy at the national/regional and at the European level at an early stage in the life-cycle of therapies which interventions are currently undergoing clinical trials,
- to monitor (ongoing studies and their results) permanently - in the format of a Living Document - potential therapies against covid-19,
- to present comparative data on effectiveness and safety of potential therapies and
- to support preparations for an evidence-based purchasing of regional/ national health politicians, if necessary.

To avoid redundancies and duplication, the EUnetHTA Rolling Collaborative Review will reuse sources from international initiatives to collect information and data on Covid-19 treatments.

The scope of the Rolling Collaborative Review is of descriptive nature. These **EUnetHTA Rolling Collaborative Reviews are not meant to substitute a joint Relative Effectiveness Assessment (REA)** adhering to the agreed procedures and aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the (prospective) Marketing Authorization Holder (MAH).

2 METHODS

This Rolling Collaborative Review is prepared according to the project plan ("Rolling Collaborative Review (RCR) on Covid-19 treatments: Project description and planning", published on the EUnetHTA website) and will be updated monthly. Monthly updates are published on the EUnetHTA Covid-19 Website (https://eunethta.eu/services/covid-19/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**Disease** • SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** (https://www.who.int/classifications/icd/covid19/en) • An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. • An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. • Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. • In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms** • COVID-19, Coronavirus Disease 2019 **Target population** (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)

	• Asymptomatic or pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms. • Mild Illness: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging. • Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level. • Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%. • Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.
Intervention	Interferon beta-1a (IFN β-1a) alone or in combination with other treatments or standard of care or Novaferon (Nova) alone or in combination with other treatments or standard of care.
Comparison	Any active treatment, placebo, or standard of care. **Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
Outcomes	<u>Main outcome:</u> • All-cause Mortality (Survival) <u>Additional Outcomes:</u> Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.
Study design	Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)

2.2 Sources of information

According to the project plan, this Rolling Collaborative Review is based on three main sources of information, as described below:

1. Summary of findings (SoF) table for published RCTs related to effectiveness and safety:

This table is based on the living systematic review and Network Meta-Analysis (NMA) created by the partnering institute of DEPLazio: find the PROSPERO protocol here. DEPLazio provides updates for the SoF table on a monthly basis to the EUnetHTA partners authoring the respective Rolling CR documents who are integrating this information accordingly.

The literature search is conducted in the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

Population	People affected by COVID-19, as defined by the authors of the studies. No limits in terms of gender or ethnicity. SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. It started spreading in December 2019, and was declared a pandemic by the World Health Organisation on 11th March 2020. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death.
Intervention	Interventions for the treatment of people affected by COVID-19, including pharmacological interventions (e.g. antibiotics, antibodies, antimalarial, antiviral, antiretroviral, immune-suppressors/modulators, kinase inhibitors) and their combinations.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	All-cause mortality Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO2/FiO2, Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events.
Study design	Randomised controlled trials (RCT); no restriction on language of publication

To identify preprints of preliminary reports of work that have not been peer-reviewed, the following sources are searched:

- medRxiv Health Sciences
- bioRxiv Biology

In addition to the sources and strategies described above, registers of ongoing studies are screened. Key conferences and conference proceedings are considered.

Data extraction, Risk of bias assessment, data synthesis:

Two reviewers from DEPLazio are screening search results, assessing full texts of studies and extract study characteristics and outcome data according to pre-defined criteria.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [1].

Dichotomous outcomes are analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI).Continuous outcomes are analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome.

The standardised mean difference (SMD) is applied when studies used different instruments. Pairwise meta-analyses is performed for primary and secondary outcomes using a random-effects model in RevMan for every treatment comparison [2]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [3].

- Sources: http://deplazio.net/farmacicovid/index.html for SoF (or https://covid-nma.com/)

2. Table(s) on published (peer reviewed) observational studies for safety results:

The literature search is conducted on a monthly basis using the following sources:

- https://www.fhi.no/en/qk/systematic-reviews-hta/map/
- https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info

Population	See project Scope
Intervention	Interferon beta-1a (IFN β-1a) alone or in combination with other treatments or standard of care or Novaferon (Nova) alone or in combination with other treatments or standard of care.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Prospective non-randomised controlled trials, prospective case series, registries Exclusion criteria: retrospective case series, case studies

One researcher carries out title and abstract screening and assesses the full texts of all potentially eligible studies. One researcher extracts the data and assesses the risk of bias using Robins-I (https://training.cochrane.org/handbook/current/chapter-25).

Results are presented in tabular form for all included studies.

3. Table(s) on ongoing trials:

The following clinical trial registries are searched on a monthly basis:

- ClinicalTrials.gov: https://clinicaltrials.gov/
- ISRCTN: https://www.isrctn.com/
- European Clinical Trials Registry: https://www.clinicaltrialsregister.eu/

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher is searching and extracting the data for the eligible studies.

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

Type 1 interferons (IFN–1) are a group of cytokines comprising the α and β subtypes (themselves subdivided in several isoforms), as well as the ε, ω and κ subtypes [4]. They are secreted by different cell types including plasmacytoid dendritic cells, upon recognition of viral components [5]. IFN-1 play a major role in antiviral immunity, and they are among the first cytokines produced during a viral infection. They are recognized by the IFNAR receptor present on the plasma membrane in most cell types. Interferon binding to IFNAR induces activation of interferon-stimulated genes (ISG). Most ISGs are involved in inflammation, signalling and immunomodulation. They slow viral replication and spread by several mechanisms such as a slowdown of cell metabolism or secretion of cytokines, which promote the activation of the adaptive immunity. ISGs also sensitize the cell to pathogens, proteins which decrease membrane fluidity, preventing viral egress or membrane fusion, and antivirals that specifically inhibit one step of the viral cycle [6, 7]. Because of their immunomodulatory properties, IFN-1 are used to treat numerous diseases such as multiple sclerosis [8]. Therapeutic forms of IFN- β can be produced in bacterial expression systems, i.e. IFN- β 1b, or in mammalian cells, i.e. IFN β-1a [9]. Besides its antiviral properties, IFN β-1a improves acute respiratory distress syndrome (ARDS) complications [10].

Novaferon is a novel protein drug that exhibits broad-spectrum antiviral properties [11]. Novaferon consists of 167 amino acids and is not a naturally existing protein. According to the published information in a US patent (US 7,625,555 B2), this protein has been produced in laboratory on the technical basis of DNA shuffling technology and named Novaferon by its inventors [12]. Novaferon has similar properties of IFN-I but its antiviral activities has been greatly improved being at least 10 times more potent than human interferon α -2b [13].

3.2 Regulatory Status

Human IFN-β was initially approved by the FDA in 1993 in the management of relapsing forms of Multiple Sclerosis (MS) [14]. IFN β-1a is produced by CinnaGen Co Iran (used in one of the included RCTs in this RCR), under the brand name ReciGen® under EU GMP license [15].

The antiviral efficacy of Novaferon was demonstrated by clinical studies conducted in China [12]. In April 2018, Novaferon (Nova) was approved in China by the former CFDA (Chinese Food and Drug Administration) for the treatment of chronic hepatitis B [11]. Novaferon's non-proprietary name was initially "recombinant cytokine gene-derived protein injection" given by Chinese Pharmacopeia Committee, and the recommended international non-proprietary name (rINN) by WHO is not available yet.

3.3 Level of Evidence

Both IFN β-1a and Novaferon are being evaluated in two small RCTs [11, 16]. Moreover, 9 ongoing studies are reported in international clinical trial registries.

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

An Iranian RCT [16] including 92 patients evaluated the effects of IFN β-1a (n=46) compared to standard treatment (n=46) in COVID-19 patients. The authors reported significantly higher discharge rate and lower mortality rate in the IFN β-1a -group at 14 days. The certainty on the evidence was very low.

One Chinese RCT [11] with three arms including 89 patients has evaluated the effect of Novaferon (n=30), Lopinavir/Ritonavir (n=29) and Novaferon + Lopinavir/Ritonavir (n=30) in COVID-19 patients. The groups treated with Novaferon alone or in combination with Lopinavir/Ritonavir showed significantly

higher clearance rates on day 6 than the group treated with Lopinavir/Ritonavir alone, but the certainty on the evidence is very low. No serious adverse events were reported.

Source: http://deplazio.net/farmacicovid/index.html

4.2 Safety evidence from observational studies

We identified no observational studies that met the inclusion criteria. We searched in the electronic databases on the 27th September and exported the retrieved references to Covidence. The use of a retrospective design and small sample size represented the most common reasons for exclusion.

A case series study conducted in China, documented the treatment of 135 hospitalized patients who received traditional Chinese medicine alongside antiviral therapy (Kaletra or interferon), corticosteroids, and antibacterial treatment. We excluded this study as it did not specify the type of interferon that was provided to the patients [17].

Sources: https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info
https://www.fhi.no/en/qk/systematic-reviews-hta/map/

4.3 Ongoing studies

Currently there are nine ongoing RCTs evaluating the effects of IFN β-1a alone or in combination with other therapies in the treatment of COVID-19. The trials are mainly in phase II or III and involve hospitalized patients with mild to severe symptoms. Only one British study also followed home-based patient treatment after discharge (ISRCTN14241621). Main outcomes include all-cause mortality, duration of ICU stay and time to recovery or clinical improvement.

Sources:
https://clinicaltrials.gov/
https://www.isrctn.com/
https://www.clinicaltrialsregister.eu/

4.4 Scientific conclusion about status of evidence generation

The body of evidence on the clinical effect and safety of IFN β-1a and Novaferon is poor, and any solid conclusion is constrained due to the very low certainty on the findings from the randomized trials. No safety data form observational studies are available. An important number of trials with large populations are ongoing, which might plausibly strengthen the knowledge on these substances for the treatment of people affected by COVID-19.

Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of IFN β-1a and Novaferon

***Source**: Crescenzo F, Amato L, Vecchi S, D'Alo' GL, Cruciani F, Mitrova Z, Saulle R, Addis A, Davoli M. Comparative effectiveness of pharmacological interventions for Covid-19: a living systematic review and network meta-analysis. PROSPERO 2020: CRD42020176914.*

IFN β-1a versus standard treatment

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk/mean (SD) standard treatment	Risk/mean (SD) IFN β-1a				
All-cause mortality at end of treatment (14 days)	304 per 1000	87 per 1000	RR 0.29 (0.10 to 0.80)	216 fewer per 1000 (from 274 fewer to 61 fewer)	92	Very low
Number discharged at end of treatment (14 days)	370 per 1000	609 per 1000	RR 1.65 (1.06 to 2.56)	240 more per 1000 (from 22 more to 577 more)	92	Very low
Number with adverse events	22 per 1000	304 per 1000	RR 14.00 (1.92 to 102.13)	283 more per 1000 (from 20 more to 1.000 more)	92	Very low
Duration of ICU admission (days)	8,52 (7,48)	7,71 (8,75)	-	SMD 0.1 lower (0.51 lower to 0.31 higher) in intervention group	92	Very low
Duration of hospitalization (days)	12,25 (7,48)	14,80 (8,45)	-	SMD 0.32 higher (0.09 lower to 0.73 higher) in intervention group	92	Very low

Explanations of GRADE: Level of certainty was downgraded of two levels for high risk of performance and attrition bias and unclear risk for selection and reporting bias, and further downgraded of one level for small sample size

Source (study): Davoudi-Monfared E, Rahmani H Khalili H al. et. Efficacy and safety of interferon beta-1a in treatment of severe COVID-19: A randomized clinical trial. medRxiv. DOI: https://doi.org/10.1101/2020.05.28.20116467 [16]

Novaferon versus Lopinavir/Ritonavir

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with Lopinavir/ Ritonavir	Risk with Novaferon				
SARS-CoV-2 clearance	517 per 1000	567 per 1000	RR 1.10 (0.68 to 1.75)	52 more per 1000 (from 166 fewer to 388 more)	59	Very low
Progression of COVID-19 severity	143 per 1000	0 per 1000	RR 0.11 (0.01 to 1.97)	127 fewer per 1000 (from 141 fewer to 139 more)	56	Very low
Number with adverse events	138 per 1000	0 per 1000	RR 0.11 (0.01 to 1.91)	123 fewer per 1000 (from 137 fewer to 126 more)	59	Very low

Explanations of GRADE: Level of certainty was downgraded of one level for high risk of performance bias and unclear risk of selection bias, and further downgraded of two levels for very few events and small sample size

Source (study): Zheng F, Zhou Y, Zhou Z, et al. A Novel Protein Drug, Novaferon, as the Potential Antiviral Drug for COVID-19. MedRxiv. 2020. DOI: https://doi.org/10.1101/2020.04.24.20077735 [11].

Novaferon versus Novaferon + Lopinavir/Ritonavir

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with Novaferon + Lopinavir/ Ritonavir	Risk with Novaferon				
SARS-CoV-2 clearance	700 per 1000	567 per 1000	RR 1.24 (0.84 to 1.83)	136 more per 1000 (from 91 fewer to 470 more)	60	Very low
Number with adverse events	100 per 1000	0 per 1000	RR 7.00 (0.38 to 129.93)	0 fewer per 1000 (from 0 fewer to 0 fewer)	60	Very low
Number with severe adverse events	Serious adverse events were not reported in either group.					Low
Progression of COVID-19 severity	None of the patients, with a moderate disease severity, had worsened disease.					Low

Explanations of GRADE: For the outcomes “SARS-CoV-2 clearance” and “Number with adverse events”, the level of certainty was downgraded of two levels for very few events and small sample size, and further downgraded of one level for small sample size. For the outcomes “Number with severe adverse events” and “Progression of COVID-19 severity”, the level of certainty was downgraded of one level for high risk of performance bias and unclear risk of selection bias, and further downgraded of one level for small sample size

Source (study): Zheng F, Zhou Y, Zhou Z, et al. A Novel Protein Drug, Novaferon, as the Potential Antiviral Drug for COVID-19. MedRxiv. 2020. DOI: https://doi.org/10.1101/2020.04.24.20077735 [11].

Table 4-2 Ongoing trials of single agents IFN β-1a and Novaferon

Active substance	**IFN β-1a**	**IFN β-1a**	**IFN β-1a**	**IFN β-1a**
Sponsor	IRCCS San Raffaele	University of Oxford	University Medical Center Utrecht	Synairgen Research Ltd
Trial Identifier	NCT04449380	ISRCTN50189673 NCT04381936 2020-001113-21	ISRCTN67000769 NCT02735707 2015-002340-14	ISRCTN14241621 NCT04385095 2020-001023-14
Phase & Intention	Phase 2 trial to test the efficacy of IFN-β-1a in COVID-19 patients	Phase 2/3 to compare several different treatments that may be useful for patients with COVID-19.	Phase: not reported. To generate evidence that can be used to reduce mortality, ICU use and morbidity in patients who are severely ill from community-acquired pneumonia and/or COVID-19.	Phase 2 to test if IFN β-1a (SNG001) can prevent/limit the worsening of lower respiratory tract illness.
Study design	Open label RCT	Randomised adaptive trial	RCT	Multicentre double blinded RCT
Status of trial	Not yet recruiting	Recruiting	Recruiting	Recruiting
Duration/End of Study	Estimated Study Start Date: September 2020 Estimated Primary Completion Date: April 2021 Estimated Study Completion Date: June 2021	March 2020 through the duration of the current COVID-19 epidemic	April 2016 to December 2023	March 2020 to May 2021
Number of Patients	126 (> 18 years old)	15 000 (no age limits)	1 000 (adults)	Hospital: 100 (>18 years old) Home: 120 (>18 years old)
Disease severity	Pneumonia; clinical status defined as 3, 4 or 5 on the 7-point ordinal scale	Hospitalized, mild to severe	Critically ill from community-acquired pneumonia and/or COVID-19	Severe enough to have caused admission to hospital
Setting	Hospital	Hospitals	Hospitals	Hospitals and home
Country	Italy	United Kingdom	International, 134 intensive care units	United Kingdom
Intervention drug name and dosage	IFNβ-1a administered subcutaneously at a dose of 44 mcg, three times per week at least 48 hours apart, for a total of two weeks. All patients will receive a total dose of 264 mcg under physician control	IFN-β1a: Nebulized solution of IFN-β1a 6 MIU (0.5ml of a solution containing 12 MIU/ml) once daily for 10 days or until discharge	IFNβ-1a, dosage not reported.	SNG001 nebuliser solution is presented in glass syringes containing 0.65 ml of drug product solution containing 12 MIU/ml of IFN-β1a. The I-neb nebuliser is fitted with a 0.53 ml chamber is filled with the contents of one syringe. The Ultra device is filled with the

Active substance	IFN β-1a	IFN β-1a	IFN β-1a	IFN β-1a
				contents of two syringes. Patients inhale one dose per day for 14 days.
Comparator (drug name and dosage)	Standard of care: any pharmacological (e.g. antibiotics, etc.) and non-pharmacological (e.g. oxygen, ventilation, etc.) treatments prescribed on clinical grounds	1. Standard care 2. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 hours for 10 days or until discharge 3. Corticosteroid (dexamethasone): administered as an oral (liquid or tablets) or intravenous preparation 6 mg once daily for 10 days or until discharge 4.Hydroxychloroquine by mouth for a total of 10 days	1. No immune modulation (no placebo) 2. Anakinra 3. Tocilizumab 4. Sarilumab	The placebo will be the same formulation as the study medication but without IFN-β1a (i.e. only the excipients of the SNG001 solution) and will be administered once daily via the I-neb or Ultra nebulizer.
Duration of observation/ Follow-up	29 days	Until death, discharge from hospital or 28 days after randomisation (whichever is sooner). Longer-term (up to 10 years) follow-up will be sought through linkage to electronic healthcare records and medical databases.	Duration of hospital stay up to 90 days. Follow-up at 6 months where feasible.	14 days of treatment + the following 14 days (+/- 3 days) after the patient's last dose or when the last dose of study medication would have been administered if dosing was stopped.
Endpoints Primary Outcomes	Time to negative conversion of SARS-CoV-2 nasopharyngeal swab.Time Frame: from baseline to day 29	All-cause mortality at 28 days after randomisation	The number of days alive and not requiring ICU organ support measured at day 21	Change in condition measured using the Ordinal Scale for Clinical Improvement during the dosing period - minimum of 0 (patient is well) to a maximum of 8 (death). Time Frame: day 1 to day 15 daily and on day 28
Results/Publication	Not provided	Not provided	Not provided	Not provided

Table 4-3 Ongoing trials of combination therapies IFN β-1a and Novaferon

Active substance	IFN β-1a + Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine	Hydroxychloroquine + Lopinavir / Ritonavir + IFN β-1a	Lopinavir/ritonavir + interferon beta	High dose IFN β-1a + Lopinavir /Ritonavir	Remdesivir plus IFN β-1a
Sponsor	Shahid Beheshti University of Medical Sciences	Shahid Beheshti University of Medical Sciences	World Health Organization	Shahid Beheshti University of Medical Sciences	National Institute of Allergy and Infectious Diseases (NIAID)
Trial Identifier	NCT04350671	NCT04343768	ISRCTN83971151	NCT04521400	NCT04492475
Phase & Intention	Phase 4 trial to compare the effects of adding IFNβ-1a to a control of Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine in patients with moderate to severe COVID-19	Phase 2 trial to determine the effects of IFNβ-1a compared to IFNβ-1b and the base therapeutic regiment in moderate to severe COVID-19	Phase III to discover whether treatment with any of the following substances help treat COVID-19; remdesivir, chloroquine or hydroxychloroquine, lopinavir plus ritonavir, and interferon-beta.	Phase 2 trial to determine the effects of high-dose IFNβ-1a compared to low-dose IFN β-1a in moderate to severe Covid-19	Phase 3 trial to evaluate the effects of the combination of IFNβ-1a and remdesivir compared to remdesivir alone in hospitalized adults diagnosed with COVID-19
Study design	Double-blind, placebo-RCT	RCT with parallel assignment	Open-label randomized multicountry clinical trial	RCT with parallel assignment	Double-blind, placebo-RCT
Status of trial	Recruiting	Completed	Recruiting	Not yet recruiting	Recruiting
Duration/End of Study	Estimated study completion date: April 24, 2020 (no further data reported)	Study Start Date: April 9, 2020 Study Completion: April 27, 2020	01/03/2021 to 25/03/2021	Estimated Study Start Date: August 20, 2020 Estimated Primary Completion Date: September 4, 2020 Estimated Study Completion Date: September 11, 2020	Actual Study Start Date: August 4, 2020 Estimated Primary Completion Date: November 1, 2023 Estimated Study Completion Date: November 1, 2023
Number of Patients	40 (> 50 years old)	60 (> 18 years old)	It is anticipated that at least several thousand patients will be recruited into the trial. (>18 years old)	100 (> 18 years old)	1038 (18-99 years old)
Disease severity	Moderate to severe	Moderate to severe	Hospitalized, mild to severe	Moderate to severe	Moderate to severe
Setting	Hospital	Hospital	Hospitals	Hospital	Hospital (multicentre)
Country	Iran	Iran	International	Iran	USA
Intervention drug name and dosage	IFN β-1a+ Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine	Hydroxychloroquine + Lopinavir / Ritonavir + IFN β-1a	Kaletra (orally twice daily for 14 days) plus IFN β-1a (daily injection for 6 days)	High dose IFN β-1a (Recigen) (Subcutaneous injections	Remdesivir plus IFN β-1a: 200 mg of Remdesivir administered intravenously

Active substance	IFN β-1a + Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine	Hydroxychloroquine + Lopinavir / Ritonavir + IFN β-1a	Lopinavir/ritonavir + interferon beta	High dose IFN β-1a + Lopinavir /Ritonavir	Remdesivir plus IFN β-1a
	Dosage not reported			of 88µg (24,000 IU) on days 1, 3, 6) + Lopinavir/Ritonavir (Kaletra) [IFN β-1a group] (400mg/100 mg twice a day for 10 days	on Day 1, followed by a 100 mg once-daily maintenance dose of Remdesivir while hospitalized for up to a 10-day total course and 44 mcg of IFN β-1aadministered by a 0.5 mL subcutaneous injection on Days 1, 3, 5, and 7 while hospitalized for a total of 4 doses.
Comparator (drug name and dosage)	Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine Dosage not reported	Hydroxychloroquine + Lopinavir / Ritonavir + IFN β-1b Hydroxychloroquine + Lopinavir / Ritonavir	Local standard of care alone OR local standard of care plus one of: 2. Remdesivir (daily infusion for 10 days) 3. Chloroquine or hydroxychloroquine (two oral loading doses, then orally twice daily for 10 days) 4. Kaletra (orally twice daily for 14 days)	Low dose IFN β-1a (Recigen) (Subcutaneous injections of 44µg (12,000 IU) on days 1, 3, 6) + Lopinavir/Ritonavir (Kaletra) [IFN β-1agroup] (400mg/100 mg twice a day for 10 days	The IFN β-1a placebo contains either 0.5 mL 0.9% normal saline or 0.5 mL sterile water for injection. Remdesivir is also administrated.
Duration of observation/ Follow-up	14 days after randomization	14 days after randomization	Until death or discharge from hospital	14 days after randomization	29 days
Endpoints Primary Outcomes	Time to clinical improvement [Time Frame: From date of randomization until 14 days later]. Improvement of two points on a seven-category ordinal scale (recommended by the World Health Organization: Coronavirus disease	Time to clinical improvement [Time Frame: From date of randomization until 14 days later]. Improvement of two points on a seven-category ordinal scale (recommended by the	All-cause mortality, subdivided by the severity of disease at the time of randomization, measured using patient records throughout the study	Time to clinical improvement [Time Frame: From date of randomization until 14 days later]. Improvement of two points on a seven-category ordinal scale (recommended by the	Time to recovery [Time Frame: Day 1 through Day 29] Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale: 1) Hospitalized, not requiring

Active substance	IFN β-1a + Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine	Hydroxychloroquine + Lopinavir / Ritonavir + IFN β-1a	Lopinavir/ritonavir + interferon beta	High dose IFN β-1a + Lopinavir /Ritonavir	Remdesivir plus IFN β-1a
	(COVID-2019) R&D. Geneva: World Health Organization) or discharge from the hospital, whichever came first.	World Health Organization: Coronavirus disease (COVID-2019) R&D. Geneva: World Health Organization) or discharge from the hospital, whichever came first.		World Health Organization: Coronavirus disease (COVID-2019) R&D. Geneva: World Health Organization) or discharge from the hospital, whichever came first.	supplemental oxygen and no longer requires ongoing medical care; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Not hospitalized, no limitations on activities.
Results/Publication	Not provided	Not provided	Not provided	Not provided	Not provided

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