EUnetHTA Joint Action 3 WP4

"Rolling Collaborative Review" of Covid-19 treatments

INTERFERON (IFN) AND NOVAFERON (NOVA) FOR THE TREATMENT OF COVID-19

Project ID: RCR13
Monitoring Report

Version 4.0, December 2020

Template version November 2020

This Rolling Collaborative Review Living Document is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020)

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 0.1	**01/09/2020**	Literature searches, Literature screening, Data extraction
V 0.2	**02/09/2020**	Data extraction and analysis complete
V 0.3	**03/09/2020**	Check of data extraction and analysis
V 1.0	**15/09/2020**	First version
V 1.1	**28/09/2020**	Literature searches, Literature screening, Data extraction
V 1.2	**01/10/2020**	Data extraction and analysis complete
V 1.3	**12/10/2020**	Check of data extraction and analysis
V 2.0	**15/10/2020**	Second version
V 3.0	**15/11/2020**	Third version
V 4.0	**15/12/2020**	Fourth version

Major changes from previous version

Chapter, page no.	Major changes from version 3.0
Effectiveness and Safety evidence from RCTs, p.11	Additional studies included
Ongoing studies, p. 12	Additional trials included

Disclaimer

The content of this “Rolling Collaborative Review” (RCR) represents a consolidated view based on the consensus within the Authoring Team; it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA’s participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

Rolling Collaborative Review team

Author(s)	Division for Health Services, Norwegian Institute of Public Health (NIPHNO), Norway
Co-Author(s)	Department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy

Further contributors

Project Management	
Zorginstituut Nederland (ZIN), Netherlands	Coordination between involved parties throughout the assessment
Austrian Institute for Health Technology Assessment (AIHTA), Austria	Coordination of RCR

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).

Copyright

How to cite this assessment

Please cite this assessment as follows:

EUnetHTA Rolling Collaborative Review (RCR13) Authoring Team. [Interferon (IFN) and Novaferon (Nova) for the treatment of COVID-19]. Diemen (The Netherlands): EUnetHTA; 2020. [date of citation]. 64 pages. Report No.: RCR13. Available from: https //www.eunethta.eu.

Contact the EUnetHTA Secretariat EUnetHTA@zinl.nl with inquiries about this assessment.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

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	Any form of Interferon (IFN) 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	Main outcome: • All-cause Mortality (Survival) Additional Outcomes: 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. Appendix Table 6-1 describes in detail the sources searched, the search terms used and the dates at which the searches are executed.

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. The process of study selection is depicted as a flow diagram in Appendix Figure 6-1.

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/

Search methods are described in more detail in Appendix Table 6-2.

Population	See project Scope
Intervention	Any form of Interferon (IFN) 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	Inclusion criteria: Prospective non-randomised controlled trials, prospective case series (i.e. comparative or single-arm prospective studies), registries Exclusion criteria: retrospective studies, case studies/ case reports, observational studies that do not report safety data

Two researchers from NIPHNO carry out title and abstract screening and assess the full texts of all potentially eligible studies. The study selection process is depicted in a flow diagram (Appendix Figure 6-2).
One researcher of NIPHNO 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 of NIPHNO is searching and extracting the data for the eligible studies. At the drafting stage of each update, the author team verifies whether the status of previously identified studies has changed. This is done by verifying the date of the last update posted in the trial registers. In addition, trial register IDs of all previously identified studies are entered in both PubMed and Google

(google.com) to verify if previously identified studies have been published since the last update. In Google, the first 10 hits are screened for this purpose.

Search methods are described in more detail in Table 6-3.

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, 16]. 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

Ten RCTs have documented the effectiveness and safety of IFN and Novaferon [11, 17-26]. Moreover, 27 ongoing studies are reported in international clinical trial registries.

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

To date, eleven RCTs have studied the effectiveness and safety of IFN or Novaferon for COVID-19, providing data for the following 13 comparisons:

1. IFNβ-1a versus standard treatment: three RCTs [17, 21, 24]
2. IFNβ-1b versus standard treatment: one RCT [22]
3. IFNα-2b versus standard treatment: one RCT [20]
4. IFNα-2b + IFN Gamma versus IFNα-2b: one RCT [20]
5. Lopinavir / Ritonavir + Ribavirin + IFNβ-1b versus Lopinavir / Ritonavir: one RCT [19]
6. Favipiravir + IFNβ-1b versus Hydroxychloroquine: one RCT [26]
7. Ribavirin + IFNα versus Ribavirin + Lopinavir / Ritonavir + IFNα: one RCT [18]
8. Ribavirin + Lopinavir / Ritonavir + IFNα versus Lopinavir / Ritonavir + IFNα: one RCT [18]
9. Lopinavir / Ritonavir + IFNα versus Ribavirin + IFNα: one RCT [18]
10. Leflunomide + IFNα-2a versus IFNα-2a: one RCT [23]
11. Novaferon versus Lopinavir/Ritonavir: one RCT [11]
12. Novaferon + Lopinavir / Ritonavir versus Novaferon: one RCT [11]
13. Peginterferon lambda 1a versus Placebo: one RCT [25]

Overall, apart from the comparison between Lopinavir / Ritonavir + Ribavirin + IFNβ-1b versus Lopinavir / Ritonavir [19], the certainty on the body of evidence varied between low and very low for all the outcome measures reported in the eight RCTs. The most reported outcomes were mortality and adverse events (nine comparisons), and discharge rates at the end of treatment (four comparisons). See Table 4-1 for further details. Characteristics of the included RCTs are presented in Table 4-2 to Table 4-4.

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 30th November 2020 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 [27]. Besides, we excluded a prospective multicentre observational study published in Spain by Taboada and colleagues [28] because only 38 patients (39% of the sample size) received IFN, and therefore will be fully will fully describe it in the RCRs on Lopinavir/Ritonavir and Tocilizumab, since 93% of the participants received this treatment.

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 27 ongoing RCTs evaluating the effects of different forms of IFN alone or in combination with other therapies in the treatment of COVID-19 (see Table 4-5 to Table 4-12). IFN β-1a is the most common form of IFN being studied. The trials are mainly in phase II or III and involve hospitalized patients with mild to severe symptoms. Main outcomes include all-cause mortality, time to recovery or clinical improvement, and duration of ICU stay. Different forms of IFN are under study in the ongoing studies, as follows:

- IFN-α (single and in combination): 5 ongoing studies
- IFN β-1a and Novaferon (single agents): 8 ongoing studies
- IFN β-1a and Novaferon (combination therapies): 6 ongoing studies
- IFN β-1b (single and in combination): 4 ongoing studies
- IFN Lambda (single and in combination): 4 ongoing studies

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 effects and safety of IFN and Novaferon (Nova) is weak, and any solid conclusion is constrained due to the low and very low certainty of the findings from the RCTs. 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 and Novaferon

***Source**: De 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.*

IFNβ-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 (28 days) [1,2,3]	110 per 1000	117 per 1000	RR 0.69 (0.30 to 1.61)	34 fewer per 1.000 (from 77 fewer to 67 more)	4290	Very low
All-cause mortality at end of treatment (14 days) [2]	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
All-cause mortality mild/moderate patients[1]	92 per 1000	98 per 1000	RR 1.07 (0.88 to 1.31)	6 more per 1.000 (from 11 fewer to 28 more)	3831	Moderate
All-cause mortality severe patients[1]	308 per 1000	396 per 1000	RR 1.29 (0.92 to 1.79)	89 more per 1.000 (from 25 fewer to 243 more)	269	Moderate
Number discharged at end of treatment (14 days) [2,3]	615 per 1000	745 per 1000	RR 1.19 (0.98 to 1.43)	117 more per 1.000 (from 12 more to 264 more)	190	Very low
Number with adverse events[2,3]	323 per 1000	426 per 1000	RR 3.14 (0.13 to 78.69)	691 more per 1.000 (from 281 fewer to 1.000 more)	92	Very low
Number with severe adverse events[3]	280 per 1000	146 per 1000	RR 0.52 (0.23 to 1.18)	134 fewer per 1.000 (from 216 fewer to 50 more)	98	Moderate
Duration of ICU admission (days) [2]	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) [2]	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
Length of stay in hospital[3]	-	-	-	Tendency to a shorter duration of hospitalization in favour of Interferon beta 1a but not gaining statistical significance HR: 1.37 (0.85-2.20) p = 0.196	-	Moderate
Progression of Covid-19 disease severity[1]	109 per 1000	109 per 1000	RR 1.00 (0.83 to 1.20)	0 fewer per 1.000 (from 19 fewer to 22 more)	3831	Moderate

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 (studies):

1. Pan H, Peto R, Karim QA, Alejandria M, Henao-Restrepo AM, García CH, et al. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. medRxiv. 2020:2020.10.15.20209817 [21].

2. 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 [17]

3. Monk PD, Marsden RJ, Tear VJ, Brookes J, Batten TN, Mankowski M, et al; Inhaled Interferon Beta COVID-19 Study Group. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med. 2020 Nov 12:S2213-2600(20)30511-7. doi: 10.1016/S2213-2600(20)30511-7. Epub ahead of print. [24]

IFNβ-1b 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 with standard treatment	Risk with IFN β-1b				
All-cause mortality at 14 days)	75 per 1000	25 per 1000	RR 0.33 (0.04 to 3.07)	50 fewer per 1000 (from 72 fewer to 155 more)	80	Low
Number discharged at end of treatment (14 days)	450 per 1000	650 per 1000	RR 1.44 (0.96 to 2.18)	198 more per 1000 (from 18 fewer to 531 more)	80	Low

Explanations of GRADE: Level of certainty was downgraded of one 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): Rahmani H, Davoudi-Monfared E, Nourian A, et al. Interferon β-1b in treatment of severe COVID-19: A randomized clinical trial [published online ahead of print, 2020 Aug 24]. Int Immunopharmacol. 2020;88:106903. doi:10.1016/j.intimp.2020.106903 [22]

IFNα-2b 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 with standard treatment	Risk with IFN α-2b				
All-cause mortality	No deaths reported	No deaths reported	-	-	-	Very low
SARS-CoV-2 clearance at 5 days	515 per 1000	767 per 1000	RR 1.49 (1.01 to 2.19)	252 more per 1000 (from 5 more to 613 more)	63	Very low
Number of patients with any adverse event	242 per 1000	333 per 1000	RR 1.38 (0.63 to 3.02)	92 more per 1000 (from 90 fewer to 490 more)	63	Very low
Number of patients discharged at 14 days	1000 per 1000	909 per 1000	RR 1.10 (0.97 to 1.24)	91 more per 1000 (from 27 fewer to 218 more)	63	Very low
Progression of COVID-19 disease	Not reported in any of the patients	Not reported in any of the patients	-	-	-	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): Idelsis E-M, Jesus P-E, Yaquelin D-R, Dania V-B, Monica B-R, Lisandra B-R, et al. Effect and safety of combination of interferon alpha-2b and gamma or interferon alpha-2b for negativization of SARS-CoV-2 viral RNA. Preliminary results of a randomized controlled clinical trial. medRxiv. 2020:2020.07.29.20164251 [20]

IFNα-2b + IFN Gamma versus IFNα-2b

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with IFNα-2b	Risk with IFNα-2b + IFN Gamma				
All-cause mortality	No deaths reported				63	Very low
SARS-CoV-2 clearance at 5 days	515 per 1000	767 per 1000	**RR 1.49** (1.01 to 2.19)	**252 more per 1.000** (from 5 more to 613 more)	63	Very low
Number of patients with any adverse event	333 per 1000	242 per 1000	**RR 1.38** (0.63 to 3.02)	**92 more per 1.000** (from 90 fewer to 490 more)	63	Very low
Number of patients discharged at 14 days	909 per 1000	1000 per 1000	**RR 1.10** (0.97 to 1.24)	**91 more per 1.000** (from 27 fewer to 218 more)	63	Very low
Progression of COVID-19 disease	No subject with progression of COVID-19 disease				63	Very low

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

Source (study): Idelsis EM, Perez-Escribano J, Duncan-Robert Y, Vazquez-Blonquist D, Bequet-Romero M et al. Effect and safety of combination of interferon alpha-2b and gamma or interferon alpha-2b for negativization of SARS-CoV-2 viral RNA. Preliminary results of a randomized controlled clinical trial. medRxiv preprint doi: https://doi.org/10.1101/2020.07.29.20164251 [20]

Lopinavir / Ritonavir + Ribavirin + IFNβ-1b 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 Lopinavir/Ritonavir + Ribavirin + IFNβ-1b				
Number of patients with adverse events	488 per 1000	477 per 1000	**RR 0.98** (0.67 to 1.43)	**10 fewer per 1.000** (from 161 fewer to 210 more)	127	Moderate
Number of patients with severe adverse events	None	24 per 1000	**RR 0.16** (0.01 to 3.87)	**20 fewer per 1.000** (from 24 fewer to 70 more)	127	Moderate
Mortality 30 days	None					Moderate
Time to SARS-CoV-2 clearance	The study reports that the group combining lopinavir / ritonavir + ribavirin and interferon beta-1C had a significantly shorter median time (7 days [IQR 5-11]) than the control group (12 days [8-15]; HR 4.37 [95% CI 1.86-10.24], p = 0.0010					Moderate
Hospital stay	The study reports that the median hospital stay was shorter in the lopinavir / ritonavir + ribavirin + interferon beta-1C group than in the lopinavir / ritonavir control group only (9 days [7-13] vs 14.5 days [9, 3-16]; HR 2.72 [1.2-6.13], p = 0.016)					Moderate

Explanations of GRADE: Level of certainty was downgraded of one level for small sample size.

Source (study): Hung I F-N, Lung K-C, Tso, E Y-K al., et al. Triple combination of interferon beta-1b, lopinavir–ritonavir and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet May 8, 2020 https://doi.org/10.1016/ S0140-6736(20)31042-4 [19]

Favipiravir + IFNβ-1b versus Hydroxychloroquine

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with Favipiravir + IFNβ-1b	Risk with Hydroxychloroquine				
All-cause mortality	114 per 1000	133 per 1000	RR 0.85 (0.28 to 2.59)	20 fewer per 1000 (from 96 fewer to 212 more)	89	Very low
Number of patients discharged	659 per 1000	689 per 1000	RR 0.96 (0.72 to 1.28)	28 fewer per 1.000 (from 193 fewer to 193 more)	89	Very low

Explanations of GRADE: Level of certainty was downgraded of one level for small sample size.

Source (study): Khamis F, Al Naabi H, Al Lawati A, Ambusaidi Z, Al Sharji M, Al Barwani U, et al. Randomized Controlled Open Label Trial on the Use of Favipiravir Combined with Inhaled Interferon beta-1b in Hospitalized Patients with Moderate to Severe COVID-19 Pneumonia. Int J Infect Dis. 2020 Nov 9:S1201-9712(20)32319-5. doi: 10.1016/j.ijid.2020.11.008. Epub ahead of print. PMID: 33181328 [26]

Ribavirin + IFNα versus Ribavirin + Lopinavir / Ritonavir + IFNα

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with Ribavirin + lopinavir / ritonavir + IFNα	Risk with Ribavirin + IFNα				
All-cause mortality	No death reported	No death reported	-	-	-	Low
SARS-CoV-2 clearance	469 per 1000	515 per 1000	RR 0.91 (0.55 to 1.49)	46 fewer per 1000 (from 232 fewer to 252 more)	65	Low
Progression of COVID-19 disease	63 per 1000	30 per 1000	RR 2.06 (0.20 to 21.64)	32 more per 1000 (from 24 fewer to 625 more)	65	Low
Number of patients with any adverse event	938 per 1000	697 per 1000	RR 1.35 (1.06 to 1.71)	244 more per 1000 (from 42 more to 495 more)	65	Low
Number of patients with serious adverse events	No serious adverse events reported	No serious adverse events reported	-	-	-	Low
Time to SARS-CoV 2 clearance	-	-	The study reports that the negative conversion time (SARS-CoV-2 clearance) from baseline to follow-up did not differ between the two HR groups: 1.39 (0.80,2.41)	-	-	Low

Explanations of GRADE: Level of certainty was downgraded of one level 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): Huang YQ, Tang SQ, Xu XL, et al. No Statistically Apparent Difference in Antiviral Effectiveness Observed Among Ribavirin Plus Interferon-Alpha, Lopinavir/Ritonavir Plus Interferon-Alpha, and Ribavirin Plus Lopinavir/Ritonavir Plus Interferon-Alpha in Patients With Mild to Moderate Coronavirus Disease 2019: Results of a Randomized, Open-Labeled Prospective Study. Front Pharmacol. 2020;11:1071. Published 2020 Jul 14. doi:10.3389/fphar.2020.01071 [18]

Ribavirin + Lopinavir / ritonavir + IFNα versus Lopinavir / ritonavir + IFNα

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with Ribavirin + Lopinavir / ritonavir + IFNα	Risk with Lopinavir / ritonavir + IFNα				
All-cause mortality	No death reported	No death reported	-	-	-	Low
SARS-CoV-2 clearance	469 per 1000	515 per 1000	**RR 0.91** (0.55 to 1.49)	**46 fewer per 1.000** (from 232 fewer to 252 more)	68	Low
Progression of COVID-19 disease	63 per 1000	30 per 1000	**RR 2.06** (0.20 to 21.64)	**32 more per 1.000** (from 24 fewer to 625 more)	68	Low
Number of patients with any adverse event	938 per 1000	697 per 1000	**RR 1.35** (1.06 to 1.71)	**244 more per 1.000** (from 42 more to 495 more)	68	Low
Number of patients with serious adverse events	No serious adverse events reported	No serious adverse events reported	-	-	-	Low

Explanations of GRADE: Level of certainty was downgraded of one 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): Huang YQ, Tang SQ, Xu XL, et al. No Statistically Apparent Difference in Antiviral Effectiveness Observed Among Ribavirin Plus Interferon-Alpha, Lopinavir/Ritonavir Plus Interferon-Alpha, and Ribavirin Plus Lopinavir/Ritonavir Plus Interferon-Alpha in Patients With Mild to Moderate Coronavirus Disease 2019: Results of a Randomized, Open-Labeled Prospective Study. Front Pharmacol. 2020;11:1071. Published 2020 Jul 14. doi:10.3389/fphar.2020.01071 [18]

Lopinavir / Ritonavir + IFNα versus Ribavirin + IFNα

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 + IFNα	Risk with Ribavirin + IFNα				
All-cause mortality	No death reported	No death reported	-	No death reported	-	Low
SARS-CoV-2 clearance	611 per 1000	515 per 1000	RR 1.19 (0.78 to 1.81)	98 more per 1000 (from 113 fewer to 417 more	68	Low
Progression of COVID-19 disease	56 per 1000	30 per 1000	RR 1.83 (0.17 to 19.29)	25 more per 1000 (from 25 fewer to 554 more	68	Low
Number of patients with any adverse event	722 per 1000	697 per 1000	RR 1.04 (0.77 to 1.40)	28 more per 1000 (from 160 fewer to 279 more)	68	Low
Number of patients with serious adverse events	No serious adverse events reported	No serious adverse events reported	-	-	-	Low

Explanations of GRADE: Level of certainty was downgraded of one level 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): Huang YQ, Tang SQ, Xu XL, et al. No Statistically Apparent Difference in Antiviral Effectiveness Observed Among Ribavirin Plus Interferon-Alpha, Lopinavir/Ritonavir Plus Interferon-Alpha, and Ribavirin Plus Lopinavir/Ritonavir Plus Interferon-Alpha in Patients With Mild to Moderate Coronavirus Disease 2019: Results of a Randomized, Open-Labeled Prospective Study. Front Pharmacol. 2020;11:1071. Published 2020 Jul 14. doi:10.3389/fphar.2020.01071 [18]

Leflunomide + IFNα-2a versus IFNα-2a

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with Leflunomide + IFNα-2a	Risk with IFNα-2a				
All-cause mortality	No death reported	No death reported	-	-	-	Very low
Progression of COVID-19 disease	No cases reported	No cases reported	-	-	-	Very low
Number of patients with any adverse event	385 per 1000	154 per 1000	RR 2.50 (0.90 to 6.96)	231 more per 1000 (from 15 fewer to 917 more	52	Very low

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

Source (study): Wang M, Zhao Y, Hu W, Zhao D, Zhang Y, Wang T, et al Treatment of COVID-19 Patients with Prolonged Post-Symptomatic Viral Shedding with Leflunomide -- a Single-Center, Randomized, Controlled Clinical Trial. Clin Infect Dis. 2020 Sep 21:ciaa1417. doi: 10.1093/cid/ciaa1417. Epub ahead of print. PMID: 32955081 [23]

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 of patients with adverse events	897 per 1000	833 per 1000	RR 0.93 (0.76 to 1.14)	63 fewer per 1.000 (from 215 fewer to 126 more)	59	Very low
Number of patients with serious adverse events	None reported	None reported	-	-	-	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 [16].

Novaferon + Lopinavir / Ritonavir versus Novaferon

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 1.000 (from 91 fewer to 70 more)	59	Very low
Progression of disease severity	0 per 1000	143 per 1000	RR 0.11 (0.01 to 1.97)	127 fewer per 1.000 (from 141 fewer to 139 more)	56	Very low
Number of patients with adverse events	833 per 1000	833 per 1000	RR 1.00 (0.80 to 1.25)	0 fewer per 1.000 (from 167 fewer to 208 more)	59	Very low
Number of patients with serious adverse events	None reported	None reported	-	No serious adverse events reported	-	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 [16]

Peginterferon lambda1a versus Placebo

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with Peginterferon	Risk with Placebo				
Time to SARS-CoV 2 clearance	-	-	The study reports that there are no differences with respect to the time to SARS-CoV 2 clearance between the two groups. HR: 0.81 [95% CI 0.56 to 1.19]	-	120	Very low
Number of patients with any adverse event	417 per 1000	350 per 1000	RR 1.19 (0.75 to 1.88)	66 more per 1.000 (from 88 fewer to 308 more)	120	Very low
Number of patients with serious adverse events	33 per 1000	33 per 1000	RR 1.00 (0.15 to 6.87)	0 fewer per 1.000 (from 28 fewer to 196 more)	120	Very low

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

Source (study): Jagannathan P, Andrews JR, Bonilla H, Hedlin H, Jacobson KB, Balasubramanian V, et al. Peginterferon Lambda-1a for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial. medRxiv. 2020:2020.11.18.20234161. [25]

Table 4-2 Study characteristics of included RCTs

Author, year, reference number/Study name/Study ID	Davoudi-Monfared, 2020 [17]	Huang, 2020 [18]	Hung 2020 [19]
Study design, study phase	Randomized controlled trial	Randomized, open-labeled, prospective clinical trial	Open label, randomized, phase 2 trial
Centres (single centre or multicentre), country, setting	Single centre, Iran, hospital	Single centre, China, hospital	Multicentre, China, six hospitals
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	81 patients/ mean age (standard deviations) in the IFN and control groups was 56 (16) and 59.5 (14) years, respectively/ males were 54.3% of patients/severe COVID-19	101 patients/mean age 42.5 (11.5) years male 46%/mild to moderate COVID-19. Subgroups: 1. Ribavirin (RBV) plus interferon-α (IFN- α) (27, 82%) 2. Lopinavir/ritonavir (LPV/r) plus IFN- α (28, 78%) 3. RBV, LPV/r plus IFN- α (21, 66%)	Combination group: 86 patients; age 51 (31 to 61); male 52% Control group: 40 patients; age 52 (33 to 62); male 56% Severity was not reported.
Inclusion criteria	Adult patients with severe COVID-19	(1) 18–65 years of age; (2) diagnosed as mild to moderate COVID-19; and (3) willing to sign informed consent.	Adult patients aged at least 18 years admitted to hospital for virologically confirmed COVID-19; a national early warning score 2 (NEWS2) of at least 1, and symptom duration of 14 days or less upon recruitment.
Exclusion criteria	Not reported	(1) were pregnant or breastfeeding women; (2) had aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5× upper normal limit, creatinine clearance <50 ml/min; (3) were allergic or intolerant to therapeutic drugs; (4) were HIV-positive patients; (5) had severe heart disease, brain disease, lung disease, kidney disease, neoplastic disease, or other systemic diseases, which may have had the potential to influence patients' adherence to the prescribed antiviral regimens; and (6) withheld informed consent.	Not reported
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled	Interferon (IFN) β-1a in addition to the national protocol medications (hydroxychloroquine plus	RBV was given by intravenous injection at a loading dose of 2 g, followed by oral doses of 400–600 mg every 8 h	Combination group: patients who were recruited and treated less than 7 days from symptom onset received a triple

Author, year, reference number/Study name/Study ID	**Davoudi-Monfared, 2020 [17]**	**Huang, 2020 [18]**	**Hung 2020 [19]**
Study design, study phase	Randomized controlled trial	Randomized, open-labeled, prospective clinical trial	Open label, randomized, phase 2 trial
Centres (single centre or multicentre), country, setting	Single centre, Iran, hospital	Single centre, China, hospital	Multicentre, China, six hospitals
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	81 patients/ mean age (standard deviations) in the IFN and control groups was 56 (16) and 59.5 (14) years, respectively/ males were 54.3% of patients/severe COVID-19	101 patients/mean age 42.5 (11.5) years male 46%/mild to moderate COVID-19. Subgroups: 1. Ribavirin (RBV) plus interferon-α (IFN- α) (27, 82%) 2. Lopinavir/ritonavir (LPV/r) plus IFN- α (28, 78%) 3. RBV, LPV/r plus IFN- α (21, 66%)	Combination group: 86 patients; age 51 (31 to 61); male 52% Control group: 40 patients; age 52 (33 to 62); male 56% Severity was not reported.
patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	lopinavir/ritonavir or atazanavir-ritonavir). Each 44-µg/ml (12 million IU/ml) dose of IFN β-1a was subcutaneously injected three times weekly for two consecutive weeks.	depending on patients' body weight, for 14 days. LPV/r was given orally at a dose of 400 mg/100 mg per dose twice per day for 14 days. IFN- α was given by atomizing inhalation at a dose of 5 million U or 50 mg per dose twice a day for 14 days. All patients in each cohort could additionally receive nasal cannula oxygen therapy, non-steroidal anti-inflammatory drugs (NSAIDs), oral or intravenous rehydration, electrolyte correction, anti-pyretics, analgesics, and anti-emetic drugs as required by their clinical conditions, as supportive treatment.	combination of 14 days of oral lopinavir–ritonavir (lopinavir 400 mg and ritonavir 100 mg) every 12 h (via nasogastric tube to intubated patients), ribavirin 400 mg every 12 h, and subcutaneous injection of one to three doses of interferon (IFN) β-1b 1 mL (8 million international units [IU]) on alternate days depending on the day of drug commencement. For those recruited and treated between days 7 and 14, IFN β-1b injection was omitted to avoid its proinflammatory effects.
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	National protocol medications.	Ribavirin (RBV) plus IFN- α Lopinavir/ritonavir (LPV/r) plus IFN- α RBV plus LPV/r plus IFN- α	Oral lopinavir–ritonavir (lopinavir 400 mg and ritonavir 100 mg) every 12 h for 14 days.

Author, year, reference number/Study name/Study ID	**Davoudi-Monfared, 2020 [17]**	**Huang, 2020 [18]**	**Hung 2020 [19]**
Study design, study phase	Randomized controlled trial	Randomized, open-labeled, prospective clinical trial	Open label, randomized, phase 2 trial
Centres (single centre or multicentre), country, setting	Single centre, Iran, hospital	Single centre, China, hospital	Multicentre, China, six hospitals
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	81 patients/ mean age (standard deviations) in the IFN and control groups was 56 (16) and 59.5 (14) years, respectively/ males were 54.3% of patients/severe COVID-19	101 patients/mean age 42.5 (11.5) years male 46%/mild to moderate COVID-19. Subgroups: 1. Ribavirin (RBV) plus interferon-α (IFN- α) (27, 82%) 2. Lopinavir/ritonavir (LPV/r) plus IFN- α (28, 78%) 3. RBV, LPV/r plus IFN- α (21, 66%)	Combination group: 86 patients; age 51 (31 to 61); male 52% Control group: 40 patients; age 52 (33 to 62); male 56% Severity was not reported.
Primary Outcome(s)	Time to reach clinical response	The difference in the interval from baseline (initiation of antiviral treatment) to SARS-CoV-2 nucleic acid negativity by nasopharyngeal swab among the three antiviral treatment groups, with each of these two tests at least 24 h apart.	Time to achieve a negative RT-PCR result for SARS-CoV-2 in a nasopharyngeal swab sample.
Patient-relevant secondary outcome(s)	Duration of hospital stay, length of intensive care unit stay, 28-day mortality, effect of early or late administration of IFN on mortality, adverse effects, and complications during the hospitalization	Differences among the three groups in the proportion of patients with SARS-CoV-2 nucleic acid negativity at day 14, the mortality rate at day 28, the proportion of patients re-classified as severe cases during the study period, the incidence of adverse events during the study period, and the proportion of therapeutic discontinuations due to adverse events during the study period.	Time to resolution of symptoms defined as a NEWS2 of 0 maintained for 24 h; daily NEWS2 and sequential organ failure assessment (SOFA) score; length of hospital stay; and 30-day mortality. Other virological endpoints included the time to achieve negative SARS-CoV-2 RT-PCR in all clinical samples, including nasopharyngeal swab, posterior oropharyngeal saliva, throat swab, stool, and urine; daily viral load changes in the first 7 days; and emergence of amino acid mutations in the *nsp*5 gene encoding a 3C-like protease. The serum cytokine response was also measured. Safety endpoints were the frequencies and duration of adverse events.
Follow-up (days, months)	Days 0, 7, 14, and 28	Days 2, 4, 7, 14, and 28	Days 7 and 30

Author, year, reference number/Study name/Study ID	Davoudi-Monfared, 2020 [17]	Huang, 2020 [18]	Hung 2020 [19]
Study design, study phase	Randomized controlled trial	Randomized, open-labeled, prospective clinical trial	Open label, randomized, phase 2 trial
Centres (single centre or multicentre), country, setting	Single centre, Iran, hospital	Single centre, China, hospital	Multicentre, China, six hospitals
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	81 patients/ mean age (standard deviations) in the IFN and control groups was 56 (16) and 59.5 (14) years, respectively/ males were 54.3% of patients/severe COVID-19	101 patients/mean age 42.5 (11.5) years male 46%/mild to moderate COVID-19. Subgroups: 1. Ribavirin (RBV) plus interferon-α (IFN- α) (27, 82%) 2. Lopinavir/ritonavir (LPV/r) plus IFN- α (28, 78%) 3. RBV, LPV/r plus IFN- α (21, 66%)	Combination group: 86 patients; age 51 (31 to 61); male 52% Control group: 40 patients; age 52 (33 to 62); male 56% Severity was not reported.
Sponsor/ lead institution	Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran. No funding was received.	National Science and Technology Major Project of China (2018ZX10302104); and the Chongqing Special Research Project for Prevention and Control of Novel Coronavirus Pneumonia (No. cstc2020jscxfyzX0005); and the Novel Coronavirus Infection and Prevention Emergency Research Project of Chongqing Municipal Education Commission (KYYJ202001).	Department of Medicine, Queen Mary Hospital

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-3 Study characteristics of included RCTs (continued)

Author, year, reference number/Study name/Study ID	Idelsis Esquivel-Moynelo, 2020 [20]	Jagannathan, 2020 [25]	Khamis, 2020 [26]	Monk, 2020, the Inhaled Interferon Beta COVID-19 Study Group [24]
Study design, study phase	Randomized controlled clinical trial	Randomized placebo-controlled trial	Randomized controlled open label trial	Randomized, double-blind, placebo-controlled, phase 2 pilot trial
Centres (single centre or multicentre), country, setting	Single centre, Cuba, hospital	Outpatient, USA	Oman, hospital	Nine UK sites
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	63 patients Treatment group: median age 50 years, IQR 19-80; male 47% Control group: median age 24 years, IQR 19-57; male 61% Severity was not reported	120 patients/the median age was 36 years (range 18-71)/male 42%/mild to moderate COVID-19	89 patients/mean age 55 (14) years/male 58%/hospitalized patients with moderate to severe COVID-19 pneumonia	
Inclusion criteria	Adult (≥19 years-old) patients with RT-PCR confirmed SARS-CoV-2, ECOG functional status ≥ 2 (Karnofsky ≥ 70%), and who volunteered by signing the informed consent	Not reported	Age between 18–75 years, confirmed SARS-CoV-2 infection by RT-PCR test on respiratory tract specimens, moderate to severe COVID-19 pneumonia according to the WHO interim guidelines case definitions (WHO/2019 nCoV/ Surveillance Case Definition /2020.1), the interval between symptoms onset and randomization is not >10 days; for female subjects: evidence of post-menopause, or, for pre-menopause subjects, negative pre-treatment serum or urine pregnancy test, eligible subjects of child-bearing age (male or female) must agree to take effective contraceptive measures (including hormonal contraception, barrier methods or abstinence) with his/her partner during the study period and for at least 7 days following the last study treatment; not participating in any other	Patients aged 18 years or older, admitted to hospital with COVID-19 symptoms. All eligible participants had to have a confirmed SARS-CoV-2 test result in a UK National Health Service (NHS) diagnostic, qualitative RT-PCR assay or a positive point of-care test (FebriDx, Lumos Diagnostics, Sarasota, FL, USA) within the previous 24 h.

Author, year, reference number/Study name/Study ID	Idelsis Esquivel-Moynelo, 2020 [20]	Jagannathan, 2020 [25]	Khamis, 2020 [26]	Monk, 2020, the Inhaled Interferon Beta COVID-19 Study Group [24]
Study design, study phase	Randomized controlled clinical trial	Randomized placebo-controlled trial	Randomized controlled open label trial	Randomized, double-blind, placebo-controlled, phase 2 pilot trial
Centres (single centre or multicentre), country, setting	Single centre, Cuba, hospital	Outpatient, USA	Oman, hospital	Nine UK sites
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	63 patients Treatment group: median age 50 years, IQR 19-80; male 47% Control group: median age 24 years, IQR 19-57; male 61% Severity was not reported	120 patients/the median age was 36 years (range 18-71)/male 42%/mild to moderate COVID-19	89 patients/mean age 55 (14) years/male 58%/hospitalized patients with moderate to severe COVID-19 pneumonia	
			interventional drug clinical study before completion of the present one.	
Exclusion criteria	Patients with each of the following characteristics were excluded: decompensated chronic diseases at the time of inclusion (severe arterial hypertension, ischemic heart disease, diabetes mellitus, etc.), with a history of autoimmune diseases, presence of hyper inflammation syndrome, serious coagulation disorders, known hypersensitivity to any of the components of the formulation under evaluation, pregnancy or lactation, and obvious mental incapacity to issue consent and act accordingly with the study.	Not reported	Age above 75, refractory nausea, vomiting, or chronic gastrointestinal disorders, inability to swallow the study drug or having undergone extensive bowel resection which may affect adequate absorption of favipiravir; severe liver disease: underlying liver cirrhosis or alanine amino-transferase (ALT)/aspartate aminotransferase (AST) elevated over 5 times the upper limit of normal; gout or history of gout or hyperuricemia; known severe renal impairment with creatinine clearance (CrCl) of <30 ml/min or having received continuous renal replacement therapy, hemodialysis or peritoneal dialysis, known allergy or hypersensitivity to favipiravir, or pregnant or lactating women.	Inability to use a nebuliser with a mouthpiece (eg, ventilated patients and patients in intensive care); and pregnancy or intention to become pregnant and breastfeeding.

Author, year, reference number/Study name/Study ID	Idelsis Esquivel-Moynelo, 2020 [20]	Jagannathan, 2020 [25]	Khamis, 2020 [26]	Monk, 2020, the Inhaled Interferon Beta COVID-19 Study Group [24]
Study design, study phase	Randomized controlled clinical trial	Randomized placebo-controlled trial	Randomized controlled open label trial	Randomized, double-blind, placebo-controlled, phase 2 pilot trial
Centres (single centre or multicentre), country, setting	Single centre, Cuba, hospital	Outpatient, USA	Oman, hospital	Nine UK sites
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	63 patients Treatment group: median age 50 years, IQR 19-80; male 47% Control group: median age 24 years, IQR 19-57; male 61% Severity was not reported	120 patients/the median age was 36 years (range 18-71)/male 42%/mild to moderate COVID-19	89 patients/mean age 55 (14) years/male 58%/hospitalized patients with moderate to severe COVID-19 pneumonia	
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Subcutaneous treatment with a co-lyophilized combination of 3.0 MIU IFN-α2b and 0.5 MIU IFN-γ (HeberFERON, CIGB, Havana, Cuba), twice a week for two weeks.	a single, 180 mcg subcutaneous dose of Peginterferon Lambda-1a (Lambda)	Favipiravir 1600 mg on day 1 followed by 600 mg twice a day for a maximum of 10 days, and interferon (IFN) β-1b at a dose of 8 million IU (0.25 mg) twice a day was given for 5 days through a vibrating mesh aerogen nebulizer (Aerogen Solo).	SNG001 (6 MIU interferon β-1a) delivered via the I-neb nebuliser (Philips Respironics, Murrysville, PA, USA) once daily for up to 14 days.
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Thrice a week intramuscular injection of 3.0 MIU IFN-α2b (Heberon® Alpha R, CIGB, Havana, Cuba). Additionally, all patients received lopinavir-ritonavir (200/50 mg every 12 h) and chloroquine (250 mg every 12 h, i.e. standard of care).	Placebo (normal saline injection)	The standard arm included the care based on the national guidelines that had HCQ 400 mg twice per day on day 1, then 200 mg twice per day for 7 days.	Placebo delivered via the I-neb nebuliser (Philips Respironics, Murrysville, PA, USA) once daily for up to 14 days.
Primary Outcome(s)	The time to elimination of viral RNA and the time to progression to severe COVID-19, measured at 48, 72, 96 and 120 hours.	Duration until viral shedding cessation in days, Log Oropharyngeal viral load over time, mean change at day 14, Log viral load area under the curve through day 14, adverse events	Time from assignment to clinical recovery, the normalization of inflammatory markers and Improvement in oxygen saturation that is maintained for at least 72 h.	The change in clinical condition on the WHO Ordinal Scale for Clinical Improvement (OSCI) during the dosing period.
Patient-relevant secondary outcome(s)	Worsening of respiratory symptoms and adverse events	Duration until resolution of symptoms in days,	Deterioration/ aggravation of pneumonia (defined as SpO2 of	The change in BCSS score and the safety and tolerability of the

Author, year, reference number/Study name/Study ID	Idelsis Esquivel-Moynelo, 2020 [20]	Jagannathan, 2020 [25]	Khamis, 2020 [26]	Monk, 2020, the Inhaled Interferon Beta COVID-19 Study Group [24]
Study design, study phase	Randomized controlled clinical trial	Randomized placebo-controlled trial	Randomized controlled open label trial	Randomized, double-blind, placebo-controlled, phase 2 pilot trial
Centres (single centre or multicentre), country, setting	Single centre, Cuba, hospital	Outpatient, USA	Oman, hospital	Nine UK sites
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	63 patients Treatment group: median age 50 years, IQR 19-80; male 47% Control group: median age 24 years, IQR 19-57; male 61% Severity was not reported	120 patients/the median age was 36 years (range 18-71)/male 42%/mild to moderate COVID-19	89 patients/mean age 55 (14) years/male 58%/hospitalized patients with moderate to severe COVID-19 pneumonia	
		hospitalizations, emergency department visits,	_93 % or PaO2/ FiO2 of _300 mmHg or RR of _30/min without oxygen inhalation and requiring oxygen therapy or more advanced breath support); intensive care unit (ICU) admission rate, and mortality within 14 days of assignment.	investigational drug.
Follow-up (days, months)	48, 72, 96 and 120 hours	28 days	14 days	28 days
Sponsor/ lead institution	Hospital Military Central Luis Díaz Soto	Stanford University	Royal Hospital, Muscat, Oman. No funding was received for this study.	Funding: Synairgen Research Southampton General Hospital, Southampton, UK

Table 4-4 Study characteristics of included RCTs (continued)

Author, year, reference number/Study name/Study ID	Pan, 2020 WHO Solidarity trial consortium [21]	Rahmani, 2020 [22]	Wang, 2020 [23]	Zheng, 2020 [11]
Study design, study phase	Randomized controlled trial	Randomized controlled trial	Open label randomized controlled trial	A randomized, open label, parallel-group trial
Centres (single centre or multicentre), country, setting	Multicentre, 405 hospitals in 30 countries	Single centre, Iran, hospital	Single centre, China, hospital	Single centre, China, hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	11266 patients/ <50 years old (35%), 50-69 years old (45%), >70 years old (19%)/male 62%/severity was not reported	66 patients/the median (IQR) age of patients was 60 (50–71) years and 59% of them were male/severe COVID-19	48 patients Treatment group median age: 56 years, IQR 43 to 67.3/male 54%/COVID-19: mild (46%), moderate (37%), severe (12%) Control group median age: 55 years, IQR 48-66/male 37%/ COVID-19: mild (42%), moderate (37%), severe (17%)	89 participants Novaferon: median age 46 years, IQR 40 to 64/male 57%/ moderate COVID-19 93% Lopinavir/Ritonavir + Novaferon: median age 50 years, IQR 38 to 63/ male 43%/moderate COVID-19 93% Lopinavir/Ritonavir: median age 37 years, IQR 26 to 54/ male 41%/moderate COVID-19 97%
Inclusion criteria	Age ≥18 years, hospitalized with a diagnosis of COVID-19, not known to have received any study drug, without anticipated transfer elsewhere within 72 hours, and, in the physician's view, with no contra-indication to any study drug	Adult patients (≥18 years old) with positive PCR and clinical symptoms/signs of pneumonia (including dyspnea, cough and fever), peripheral oxygen saturation (SPO2) ≤ 93% in ambient air or arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2) < 300 or SPO2/FiO2 < 315 and lung involvement in chest imaging	(1) age 18–70 years with a diagnosis of COVID-19 conforming to Chinese guidelines; (2) hospitalized for prolonged post symptomatic viral shedding; (3) able to orally take medication; (4) if female, not pregnant; and (5) effective contraception for 7 days after taking the last medication.	Hospitalized COVID-19 patients with confirmed SARS-CoV-2 detection, clinically classified as moderate or severe, at an age over 18 years, and without comorbidity of severe heart, lung, or brain diseases.
Exclusion criteria	None reported	Patients with serious allergic reactions to IFN, history of suicide thoughts and attempts, alanine amino transferase (ALT) > 5× the upper limit of the normal range, uncontrolled underlying diseases such as neuropsychiatric disorders,	(1) presence of any condition that would not allow the protocol to be followed, including known allergy to leflunomide, use of medications that are contraindicated with leflunomide, or medications that could not be replaced or	None reported

Author, year, reference number/Study name/Study ID	Pan, 2020 WHO Solidarity trial consortium [21]	Rahmani, 2020 [22]	Wang, 2020 [23]	Zheng, 2020 [11]
Study design, study phase	Randomized controlled trial	Randomized controlled trial	Open label randomized controlled trial	A randomized, open label, parallel-group trial
Centres (single centre or multicentre), country, setting	Multicentre, 405 hospitals in 30 countries	Single centre, Iran, hospital	Single centre, China, hospital	Single centre, China, hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	11266 patients/ <50 years old (35%), 50-69 years old (45%), >70 years old (19%)/male 62%/severity was not reported	66 patients/the median (IQR) age of patients was 60 (50–71) years and 59% of them were male/severe COVID-19	48 patients Treatment group median age: 56 years, IQR 43 to 67.3/male 54%/COVID-19: mild (46%), moderate (37%), severe (12%) Control group median age: 55 years, IQR 48-66/male 37%/ COVID-19: mild (42%), moderate (37%), severe (17%)	89 participants Novaferon: median age 46 years, IQR 40 to 64/male 57%/ moderate COVID-19 93% Lopinavir/Ritonavir + Novaferon: median age 50 years, IQR 38 to 63/ male 43%/moderate COVID-19 93% Lopinavir/Ritonavir: median age 37 years, IQR 26 to 54/ male 41%/moderate COVID-19 97%
		thyroid disorders, cardiovascular diseases and also pregnant and lactating women.	stopped during the trial period; (2) pregnant or breastfeeding; (3) known other serious comorbidities, such as liver disease, cardiovascular disease, cerebrovascular disease, severe renal insufficiency, or advanced cancer; (4) had received interferon before enrollment; or (5) unwilling to participate in the study.	
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Study drugs were Remdesivir, Hydroxychloroquine, Lopinavir-Ritonavir and Interferon (given with Lopinavir, until July 4). Hydroxychloroquine and Lopinavir were discontinued for futility on June 18 and July 4, 2020, respectively; Interferon is ceasing on October 16.	IFN β-1b (250 mcg subcutaneously every other day for two consecutive weeks) along with the national protocol medications.	Leflunomide (50 mg every 12 hours, 3 consecutive times, orally; then 20 mg once daily for 8 days; a total course of 10 days) plus nebulized interferon alpha 2a (IFN-α-2a; 3 million IU each time, adding 2 mL of sterilized water, atomization inhalation twice daily for 10 days).	The approved dosage of Novaferon for hepatitis B application is the daily injection of 10 mg of protein in 1.0 ml volume per vial. Lopinavir/Ritonavir (Kaletra) was manufactured by AbbVie Inc.; each tablet contained 200 mg of Lopinavir and 50 mg of Ritonavir. The total daily doses

Author, year, reference number/Study name/Study ID	Pan, 2020 WHO Solidarity trial consortium [21]	Rahmani, 2020 [22]	Wang, 2020 [23]	Zheng, 2020 [11]
Study design, study phase	Randomized controlled trial	Randomized controlled trial	Open label randomized controlled trial	A randomized, open label, parallel-group trial
Centres (single centre or multicentre), country, setting	Multicentre, 405 hospitals in 30 countries	Single centre, Iran, hospital	Single centre, China, hospital	Single centre, China, hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	11266 patients/ <50 years old (35%), 50-69 years old (45%), >70 years old (19%)/male 62%/severity was not reported	66 patients/the median (IQR) age of patients was 60 (50–71) years and 59% of them were male/severe COVID-19	48 patients Treatment group median age: 56 years, IQR 43 to 67.3/male 54%/COVID-19: mild (46%), moderate (37%), severe (12%) Control group median age: 55 years, IQR 48-66/male 37%/ COVID-19: mild (42%), moderate (37%), severe (17%)	89 participants Novaferon: median age 46 years, IQR 40 to 64/male 57%/ moderate COVID-19 93% Lopinavir/Ritonavir + Novaferon: median age 50 years, IQR 38 to 63/ male 43%/moderate COVID-19 93% Lopinavir/Ritonavir: median age 37 years, IQR 26 to 54/ male 41%/moderate COVID-19 97%
	Remdesivir (intravenous): Day 0, 200mg; days 1-9, 100mg. Hydroxychloroquine (oral): Hour 0, four tablets; Hour 6, four tablets; Hour 12, begin two tablets twice daily for 10 days. Each tablet contained 200mg Hydroxychloroquine sulphate (155mg base/tablet; a little-used alternative involved 155mg chloroquine base/tablet). Lopinavir (oral): Two tablets twice daily for 14 days. Each tablet contained 200mg Lopinavir (plus 50mg Ritonavir, to slow hepatic clearance of Lopinavir). Other formulations were not provided, so ventilated patients received no study			(40 mg) of Novaferon were administered to patients twice per day by oxygen-driven aerosolized inhalation for 15 min of 20 mg of Novaferon (2 x 1 ml vials) diluted with saline. For patients receiving Lopinavir/Ritonavir (Kaletra), two tablets were orally taken twice per day. The aerosolized inhalation was administrated to hospitalized patients in the negative-pressure wards at the designated COVID-19 center to minimize the risk of disease transmission.

Author, year, reference number/Study name/Study ID	**Pan, 2020 WHO Solidarity trial consortium [21]**	**Rahmani, 2020 [22]**	**Wang, 2020 [23]**	**Zheng, 2020 [11]**
Study design, study phase	Randomized controlled trial	Randomized controlled trial	Open label randomized controlled trial	A randomized, open label, parallel-group trial
Centres (single centre or multicentre), country, setting	Multicentre, 405 hospitals in 30 countries	Single centre, Iran, hospital	Single centre, China, hospital	Single centre, China, hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	11266 patients/ <50 years old (35%), 50-69 years old (45%), >70 years old (19%)/male 62%/severity was not reported	66 patients/the median (IQR) age of patients was 60 (50–71) years and 59% of them were male/severe COVID-19	48 patients Treatment group median age: 56 years, IQR 43 to 67.3/male 54%/COVID-19: mild (46%), moderate (37%), severe (12%) Control group median age: 55 years, IQR 48-66/male 37%/ COVID-19: mild (42%), moderate (37%), severe (17%)	89 participants Novaferon: median age 46 years, IQR 40 to 64/male 57%/ moderate COVID-19 93% Lopinavir/Ritonavir + Novaferon: median age 50 years, IQR 38 to 63/ male 43%/moderate COVID-19 93% Lopinavir/Ritonavir: median age 37 years, IQR 26 to 54/ male 41%/moderate COVID-19 97%
	Lopinavir while unable to swallow. Interferon (mainly subcutaneous): Three doses over six days of 44µg subcutaneous Interferon-ß1a; where intravenous interferon was available, patients on high-flow oxygen, ventilators or ECMO were instead to be given 10µg intravenously once daily for six days.			
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	NA	National protocol medications (lopinavir/ritonavir or atazanavir/ritonavir plus hydroxychloroquine for 7–10 days).	Nebulized IFN-α-2a alone for 10 days.	NA

Author, year, reference number/Study name/Study ID	Pan, 2020 WHO Solidarity trial consortium [21]	Rahmani, 2020 [22]	Wang, 2020 [23]	Zheng, 2020 [11]
Study design, study phase	Randomized controlled trial	Randomized controlled trial	Open label randomized controlled trial	A randomized, open label, parallel-group trial
Centres (single centre or multicentre), country, setting	Multicentre, 405 hospitals in 30 countries	Single centre, Iran, hospital	Single centre, China, hospital	Single centre, China, hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	11266 patients/ <50 years old (35%), 50-69 years old (45%), >70 years old (19%)/male 62%/severity was not reported	66 patients/the median (IQR) age of patients was 60 (50–71) years and 59% of them were male/severe COVID-19	48 patients Treatment group median age: 56 years, IQR 43 to 67.3/male 54%/COVID-19: mild (46%), moderate (37%), severe (12%) Control group median age: 55 years, IQR 48-66/male 37%/ COVID-19: mild (42%), moderate (37%), severe (17%)	89 participants Novaferon: median age 46 years, IQR 40 to 64/male 57%/ moderate COVID-19 93% Lopinavir/Ritonavir + Novaferon: median age 50 years, IQR 38 to 63/ male 43%/moderate COVID-19 93% Lopinavir/Ritonavir: median age 37 years, IQR 26 to 54/ male 41%/moderate COVID-19 97%
Primary Outcome(s)	Effects on in-hospital mortality (ie, mortality during the original episode of hospitalization; follow-up ceased at discharge)	Time to clinical improvement	Duration of viral shedding, which was defined as the time from randomization to the first negative nucleic acid test of 5 consecutive RT-PCR results.	SARS-CoV-2 clearance rates on day six of treatment
Patient-relevant secondary outcome(s)	Initiation of ventilation and hospitalization duration	In-hospital complications and 28-day mortality	Clinical status (ie, progressive rate to severe illness), syndromes, peripheral blood cells, and biochemical parameters, C-reactive protein and inflammatory cytokines, and length of hospital stay. Safety outcomes included adverse events (AEs) that occurred during treatment, serious AEs, and premature discontinuation of treatment.	Time to SARS-CoV-2 clearance
Follow-up (days, months)	28 days	28 days	14 days	Days 3, 6, and 9
Sponsor/ lead institution	WHO Solidarity trial consortium	Tehran University of Medical Sciences	This work was supported by the National Key Research and Development Plan for the Emergency Management of	This work was supported by the National Science and Technology Major Project

Author, year, reference number/Study name/Study ID	Pan, 2020 WHO Solidarity trial consortium [21]	Rahmani, 2020 [22]	Wang, 2020 [23]	Zheng, 2020 [11]
Study design, study phase	Randomized controlled trial	Randomized controlled trial	Open label randomized controlled trial	A randomized, open label, parallel-group trial
Centres (single centre or multicentre), country, setting	Multicentre, 405 hospitals in 30 countries	Single centre, Iran, hospital	Single centre, China, hospital	Single centre, China, hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	11266 patients/ <50 years old (35%), 50-69 years old (45%), >70 years old (19%)/male 62%/severity was not reported	66 patients/the median (IQR) age of patients was 60 (50–71) years and 59% of them were male/severe COVID-19	48 patients Treatment group median age: 56 years, IQR 43 to 67.3/male 54%/COVID-19: mild (46%), moderate (37%), severe (12%) Control group median age: 55 years, IQR 48-66/male 37%/ COVID-19: mild (42%), moderate (37%), severe (17%)	89 participants Novaferon: median age 46 years, IQR 40 to 64/male 57%/ moderate COVID-19 93% Lopinavir/Ritonavir + Novaferon: median age 50 years, IQR 38 to 63/ male 43%/moderate COVID-19 93% Lopinavir/Ritonavir: median age 37 years, IQR 26 to 54/ male 41%/moderate COVID-19 97%
			Novel Coronavirus Pneumonia, China (grant number 2020YFC0845100); and the Wuhan Municipal Key Technology Project on Novel Coronavirus Pneumonia, China (grant number 2020020101010005). Renmin Hospital of Wuhan University, Wuhan, China	(2017ZX10202201, 2017ZX10202203), the National Key Research and Development Program of China (No. 2016YFD0500301), the Natural Science Foundation of Hunan Province (2018JJ2452) and Specialized Science and Technology Project of Hunan Province (2020SK3013).

Table 4-5 Ongoing trials *IFN-α, single and in combination*

Active substance	**IFN-α**	**IFN α-2b**	**IFN-α2β**	**IFN-α-2b + Hydrochloride**
Trial Identifier/registry ID(s)/contact	NCT04534725/ClinicalTrials.gov /Ronan Burder; ronan.burder@petermac.org	NCT04480138/ ClinicalTrials.gov/ Richa Vellanki, richa.vellanki@zyduscadila.com	NCT04293887/ ClinicalTrials.gov/Jianping Zhao, Zhaojp88@126.com	NCT04254874/ ClinicalTrials.gov/Qing Ning, qning@vip.sina.com
Study design, study phase	Randomized controlled trial, phase 3	Randomized controlled trial, phase 2	Randomized controlled trial, phase 1	Prospective/Retrospective, Randomized controlled cohort study, phase 4
Recruitment status	Not yet recruiting	Recruiting	Not recruiting	Recruiting
Number of Patients, Disease severity*	2 282 (cancer patients ≥ 18 years old), not yet tested positive	40 (> 18 years old), not specified	328 (> 18 years old), not specified	100 (≥ 18 years old), mild to severe
Setting (hospital, ambulatory, etc.)	Home or hospital	Hospital	Hospital and home	Hospital
Intervention (generic drug name and dosage)	Arm 1: Daily IFN-α intranasal spray for 3 months (pre-exposure prophylaxis) Arm 2: daily interferon-alpha intranasal spray for 7 days (at a higher dose than arm 1) (post-exposure prophylaxis)	Pegylated Interferon-α2b 1 mcg/kg on day 1 and day 8 after safety evaluations.	Standard treatment + recombinant human interferon α1β 10ug Bid administered by nebulization for 10 days	Abidol Hydrochloride combined with Interferon atomization Interferon (PegIFN-α-2b) atomization was added (45ug, add to sterile water 2ml, twice a day) on the basis of group I.
Comparator (standard care or generic drug name and dosage)	Arm 1: Placebo Arm 2: Placebo	Standard care	Standard treatment	Standard symptomatic support therapy (SMT) plus abidol hydrochloride (0.2g, 3 times a day).
Primary Outcome(s)	Incidence of COVID-19 in cancer patients using interferon-alpha as prophylaxis without or with known positive contact with COVID-19 (COVID-19 confirmed by qPCR from respiratory swab) [Time Frame: 3 months from baseline]. incidence of any upper or lower community acquired respiratory viral infection (define as identification of respiratory viruses such as coronavirus	Change in Clinical status of subject on a 7-point ordinal scale [Time Frame: Week 2] 1. Not hospitalized, no limitations on activities. 2. Not hospitalized, limitation on activities. 3. Hospitalized, not requiring supplemental oxygen. 4. Hospitalized, requiring supplemental oxygen. 5. Hospitalized, on non-invasive ventilation or high flow oxygen	The incidence of side effects [Time Frame: Within 14 days after enrolment] dyspnoea. The incidence of side effects [Time Frame: Within 14 days after enrollment] SPO2≤94%. The incidence of side effects [Time Frame: Within 14 days after enrollment]. Respiratory rate ≥24 breaths/min in oxygen state)	Rate of disease remission [Time Frame: two weeks] A: For mild patients: fever, cough and other symptoms relieved with improved lung CT; B: For severe patients: fever, cough and other symptoms relieved with improved lung CT, SPO2> 93% or PaO2/FiO2> 300mmHg (1mmHg=0.133Kpa); Time for lung recovery [Time Frame: two weeks]

	other than SARS-CoV-2, influenza, parainfluenza, respiratory syncytial virus, rhinovirus, adenovirus, human metapneumovirus). assessed using local standard of care testing (e.g. respiratory swabs, saliva and/or blood) [Time Frame: 28 days from baseline].	devices. 6. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). 7. Death.		Compare the average time of lung imaging recovery after 2 weeks of treatment in each group.
Sponsor/ lead institution, country (also, country of recruitment if different)	Peter MacCallum Cancer Centre, Australia	Cadila Healthcare Limited, Mexico	Tongji Hospital, China	Tongji Hospital, China

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-6 Ongoing trials *IFN-α, single and in combination (continued)*

Active substance	**IFN-α + oxygen therapy + Lopinavir/ritonavir + Traditional Chinese Medicines (TCMs) granules**
Trial Identifier/registry ID(s)/contact	NCT04251871/ClinicalTrials.gov/Rui-lin Wang, wrl7905@163.com
Study design, study phase	Randomized controlled trial, phase not available
Recruitment status	Recruiting
Number of Patients, Disease severity*	150 (14 years to 80 years (Child, Adult, Older Adult)), severity not reported
Setting (hospital, ambulatory,..)	Hospital
Intervention (generic drug name and dosage)	Conventional medicines (Oxygen therapy, alfa interferon via aerosol inhalation, and lopinavir/ritonavir) and Traditional Chinese Medicines (TCMs) granules Conventional medicines: oxygen therapy, antiviral therapy (alfa interferon via aerosol inhalation, and lopinavir/ritonavir, 400mg/100mg, p.o, bid) for 14 days. Traditional Chinese Medicines (TCMs) granules: 20g, p.o, bid, for 14 days.
Comparator (standard care or generic drug name and dosage)	Conventional medicines (Oxygen therapy, alfa interferon via aerosol inhalation, and lopinavir/ritonavir)

Active substance	**IFN-α + oxygen therapy + Lopinavir/ritonavir + Traditional Chinese Medicines (TCMs) granules**
Trial Identifier/registry ID(s)/contact	NCT04251871/ClinicalTrials.gov/Rui-lin Wang, wrl7905@163.com
Study design, study phase	Randomized controlled trial, phase not available
Recruitment status	Recruiting
	Conventional medicines: oxygen therapy, antiviral therapy (alfa interferon via aerosol inhalation, and lopinavir/ritonavir, 400mg/100mg, p.o, bid) for 14 days.
Primary Outcome(s)	The incidents of acute respiratory distress syndrome (ARDS) development [Time Frame: 14 days] The incidence rate of acute respiratory distress syndrome (ARDS) development
Sponsor/ lead institution, country (also country of recruitment if different)	Beijing 302 Hospital, China

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-7 Ongoing trials *Single agents IFN β-1a and Novaferon*

Active substance	**IFN β-1a**	**IFN β-1a**	**IFN β-1a**	**IFN β-1a**
Trial Identifier/registry ID(s)/contact	NCT04449380/ClinicalTrials.gov/ Emanuele Bosi, bosi.emanuele@hsr.it	ISRCTN50189673; NCT04381936; 2020-001113-21/ ClinicalTrials.gov/ Richard Haynes, recoverytrial@ndph.ox.ac.uk	ISRCTN67000769; NCT02735707; 2015-002340-14/ ClinicalTrials.gov/ Cameron Green, info@remapcap.org	ISRCTN14241621; NCT04385095; 2020-001023-14/ ClinicalTrials.gov/ Jody Brookes, jody.brookes@synairgen.com
Study design, study phase	Open label randomized controlled trial, phase 2	Randomized adaptive trial, phase 2/3	Randomized controlled trial, phase not reported	Multicentre double blinded randomized controlled trial, phase 2
Recruitment status	Recruiting	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	126 (> 18 years old), pneumonia; clinical status defined as 3, 4 or 5 on the 7-point ordinal scale	15 000 (no age limits), hospitalized, mild to severe	1 000 (adults), critically ill from community-acquired pneumonia and/or COVID-19	Hospital: 100 (>18 years old); home: 120 (>18 years old), severe enough to have caused admission to hospital
Setting (hospital, ambulatory,..)	Hospital	Hospitals	Hospitals	Hospitals and home

Intervention (generic 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 contents of two syringes. Patients inhale one dose per day for 14 days.
Comparator (standard care or generic 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.
Primary Outcome(s)	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
Sponsor/ lead institution, country (also country of recruitment if different)	IRCCS San Raffaele, Italy	University of Oxford, UK	University Medical Center Utrecht, International, 134 intensive care units	Synairgen Research Ltd, UK

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Active substance	**IFN β-1a**
Trial Identifier/registry ID(s)/contact	NCT04647669/ ClinicalTrials.gov/ Marvin Reid, The University of The West Indies
Study design, study phase	Randomized controlled trial, phase 3
Recruitment status	Not yet recruiting
Number of Patients, Disease severity*	100 (> 18 years old), hospitalised with definite COVID-19
Setting (hospital, ambulatory,..)	Hospital
Intervention (generic drug name and dosage)	Interferon ß-1a will be administered intravenously at the dose of 10 µg once daily for 6 days if oxygen dependent or subcutaneously at 44 ug Day 1, Day 3, and Day 6
Comparator (standard care or generic drug name and dosage)	Standard of Care: Treatment according to local hospital protocol Remdesivir: 200 mg intravenous loading dose on Day 1, and 100mg intravenous once-daily for subsequent doses from Day 2 up to Day 10. Acalabrutinib: 100 mg capsules twice daily every 12 h for 10 days taken with or without food. Interferon beta-1a: Interferon ß-1a will be administered intravenously at the dose of 10 µg once daily for 6 days if oxygen dependent or subcutaneously at 44 ug Day 1, Day 3, and Day 6
Primary Outcome(s)	Time to negative conversion of SARS-CoV-2 nasopharyngeal swab. Time Frame: from baseline to day 29
Sponsor/ lead institution, country (also country of recruitment if different)	IRCCS San Raffaele, Italy

Table 4-8 Ongoing trials *Single agents IFN β-1a and Novaferon (continued)*

Active substance	**IFN β-1a**	**IFN β-1a**	**IFN β-1a**
Trial Identifier/registry ID(s)/contact	NCT04385095/ClinicalTrials.gov/Jody Brookes, jody.brookes@synairgen.com	NCT04492475/ ClinicalTrials.gov/National Institute of Allergy and Infectious Diseases (NIAID), DMIDClinicalTrials@niaid.nih.gov	NCT04552379/ ClinicalTrials.gov/ Jose A Castro Rodriguez, jacastro17@hotmail.com
Study design, study phase	Randomised double-blind placebo-controlled trial, phase 2	Adaptive randomized double-blind placebo-controlled trial, phase 3	Cluster randomized controlled trial, phase 3
Recruitment status	Recruiting	Active, not recruiting	Not yet recruiting
Number of Patients, Disease severity*	820 (> 18 years old), hospitalized	1038 (> 18 years old), hospitalized	1240 (> 18 years old), household will be randomized
Setting (hospital, ambulatory,..)	Hospital and home	Hospital	Home
Intervention (generic drug name and dosage)	SNG001(contains IFN-β) inhalation using the I-neb device.	IFNβ-1a: Rebif (R) - 44 mcg administered by a 0.5 mL subcutaneous injection on Days 1, 3, 5, and 7 while hospitalized for a total of 4 doses.	Peginterferon: 125 micrograms of pegylated IFNß1alfa (PLEGRIDY, Biogen) administered on Study Days 1, 6 and 11 (i.e. for a total of 3 doses) via subcutaneous injection.
Comparator (standard care or generic drug name and dosage)	Placebo inhalation using the I-neb device.	Remdesivir: 200 mg administered intravenously on Day 1, followed by a 100 mg once-daily maintenance dose of Remdesivir while hospitalized for up to a 10-day total course. Placebo: The IFNβ-1a placebo contains either 0.5 mL 0.9% normal saline or 0.5 mL sterile water for injection.	Standard of Care; following national guidelines regarding self-isolation and infection prevention
Primary Outcome(s)	Ordinal Scale for Clinical Improvement [Time Frame: Day 1 to Days 15 and 28] 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 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 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.	The proportion of index cases shedding SARS-CoV-2, at Day 11, in the active arm compared to the standard of care arm. [Time Frame: Day 11] The proportion of household contacts shedding SARS-CoV-2, at Day 11, in the active arm compared to the standard of care arm. [Time Frame: Day 11]

Active substance	**IFN β-1a**	**IFN β-1a**	**IFN β-1a**
Trial Identifier/registry ID(s)/contact	NCT04385095/ClinicalTrials.gov/Jody Brookes, jody.brookes@synairgen.com	NCT04492475/ ClinicalTrials.gov/National Institute of Allergy and Infectious Diseases (NIAID), DMIDClinicalTrials@niaid.nih.gov	NCT04552379/ ClinicalTrials.gov/ Jose A Castro Rodriguez, jacastro17@hotmail.com
Study design, study phase	Randomised double-blind placebo-controlled trial, phase 2	Adaptive randomized double-blind placebo-controlled trial, phase 3	Cluster randomized controlled trial, phase 3
Recruitment status	Recruiting	Active, not recruiting	Not yet recruiting
Sponsor/ lead institution, country (also country of recruitment if different)	Synairgen Research Ltd., UK	National Institute of Allergy and Infectious Diseases (NIAID), USA	Pontificia Universidad Catolica de Chile, Chile

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-9 Ongoing trials *Combination therapies IFN β-1a and Novaferon*

Active substance	**IFN β-1a + Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine**	**Hydroxychloroquine + Lopinavir / Ritonavir + IFN β-1a or IFN β-1b**	**Lopinavir/ritonavir + IFN β-1a**	**High dose IFN β-1a + Lopinavir /Ritonavir**	**Remdesivir + IFN β-1a**
Trial Identifier/registry ID(s)/contact	NCT04350671/ClinicalTrials.gov/ Ilad Alavi Darazam	NCT04343768/ ClinicalTrials.gov/Seyed Sina Naghibi Irvani	ISRCTN83971151/ ISRCTN/Ana Maria Henao Restrepo, henaorestrepoa@who.int	NCT04521400/ ClinicalTrials.gov/ Ilad Alavi Darazam, ilad13@yahoo.com	NCT04492475/ ClinicalTrials.gov/ National Institute of Allergy and Infectious Diseases (NIAID)
Study design, study phase	Double-blind, placebo randomized controlled trial, phase 4	Parallel randomized controlled trial, phase 2	Open-label randomized multicountry controlled trial, phase 3	Parallel randomized controlled trial, phase 2	Double-blind, placebo randomized controlled trial, phase 3
Recruitment status	Enrolling by invitation	Completed	Recruiting	Not yet recruiting	Active, not recruiting
Number of Patients, Disease severity*	40 (> 50 years old), moderate to severe	60 (> 18 years old), moderate to severe	It is anticipated that at least several thousand patients will be recruited into the trial. (>18 years old), hospitalized, mild to severe	100 (> 18 years old), moderate to severe	1038 (18-99 years old), moderate to severe
Setting (hospital, ambulatory, etc)	Hospital	Hospital	Hospitals	Hospital	Hospital (multicentre)
Intervention (generic drug name and dosage)	IFN β-1a+ Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine Dosage not reported	Arm 1: Hydroxychloroquine + Lopinavir / Ritonavir + IFN β-1a Arm 2: Hydroxychloroquine + Lopinavir / Ritonavir + IFN β-1b	Kaletra (orally twice daily for 14 days) plus IFN β-1a (daily injection for 6 days)	High dose IFN β-1a (Recigen) (Subcutaneous injections 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	Remdesivir plus IFN β-1a: 200 mg of Remdesivir administered intravenously 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 (standard care or generic drug name and dosage)	Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine Dosage not reported	Hydroxychloroquine + Lopinavir / Ritonavir	Local standard of care alone OR local standard of care plus one of:	Low dose IFN β-1a (Recigen) (Subcutaneous injections of 44µg (12,000 IU) on days 1,	The IFN β-1a placebo contains either 0.5 mL 0.9% normal saline or 0.5 mL sterile water for

			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)	3, 6) + Lopinavir/Ritonavir (Kaletra) [IFN β-1agroup] (400mg/100 mg twice a day for 10 days	injection. Remdesivir is also administrated.
Primary Outcome(s)	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 (COVID-2019) R&D. Geneva: World Health Organization) or discharge from the hospital, whichever came first.	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 (COVID-2019) R&D. Geneva: World Health Organization) or discharge from the hospital, whichever came first.	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 World Health Organization: Coronavirus disease (COVID-2019) R&D. Geneva: World Health Organization) or discharge from the hospital, whichever came first.	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 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.
Sponsor/ lead institution, country (also country of recruitment if different)	Shahid Beheshti University of Medical Sciences, Iran	Shahid Beheshti University of Medical Sciences, Iran	World Health Organization, international	Shahid Beheshti University of Medical Sciences, Iran	National Institute of Allergy and Infectious Diseases (NIAID), USA

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-10 Ongoing trials *Single agents IFN β-1a and Novaferon (continued)*

Active substance	**IFN β-1a + Umifenovir + Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine + Standards of Care**
Trial Identifier/registry ID(s)/contact	NCT04350684/ClinicalTrials.gov/ Seyed Sina Naghibi Irvani
Study design, study phase	Double-blind, placebo randomized controlled trial, phase 4
Recruitment status	Enrolling by invitation
Number of Patients, Disease severity*	40 (> 18 years old), moderate to severe
Setting (hospital, ambulatory,..)	Hospital
Intervention (generic drug name and dosage)	Umifenovir + Interferon-β 1a + Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine + Standards of Care Dosage not reported
Comparator (standard care or generic drug name and dosage)	IFN-β 1a + Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine + Standards of Care
Primary Outcome(s)	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 (COVID-2019) R&D. Geneva: World Health Organization) or discharge from the hospital, whichever came first.
Sponsor/ lead institution, country (also country of recruitment if different)	Shahid Beheshti University of Medical Sciences, Iran

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-11 Ongoing trials *IFN β-1b, single and in combination*

Active substance	IFN-β	IFN β-1b + Clofazimine	IFN β-1b + Ribavirin
Trial Identifier/registry ID(s)/contact	NCT04324463/ ClinicalTrials.gov/ ACT COVID-19 Study Coordinator, ACT.ProjectTeam@PHRI.ca	NCT04465695 UW 20-463/ ClinicalTrials.gov/Ivan FN Hung, ivanhung@hku.hk	NCT04494399/ClinicalTrials.gov/ Ivan FN Hung, ivanhung@hku.hk
Study design, study phase	Randomized controlled trial, phase 3	Open label randomized controlled trial, phase 2	Open label randomized controlled trial, phase 2
Recruitment status	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	4000 (≥ 18 years old), not specified	81 (>18 years old), not specified	96 (>18 years old), hospitalized
Setting (hospital, ambulatory,..)	Home or hospital	Hospital	Hospital
Intervention (generic drug name and dosage)	Experimental: Colchicine Outpatients: 0.6 mg twice daily for 3 days, then 0.6 mg once daily for 25 days (total 28 days). Inpatients: 1.2 mg followed by 0.6 mg 2 hours later, then 0.6 mg twice daily for 28 days. Experimental: Interferon Beta Inpatients Only: 0.25 mg by subcutaneous injection on days 1, 3, 5 & 7 Experimental: Aspirin (ASA) Outpatients: 75 to 100 mg once daily for 28 days. Inpatients: 75 to 100 mg once daily for 28 days Experimental: Rivaroxaban Inpatients Only: 2.5 mg twice daily for 28 days.	Interferon β-1b Subcutaneous injection, 1mL (0.5mg; 16 million IU) for 3 days. Clofazimine Oral 100mg twice daily on day 1, then 100mg daily for 2 days. +Standard care	5-day course of daily subcutaneous injection of IFN β-1b 2mL (16 million IU) consecutively and oral ribavirin 400mg twice daily plus standard care + 5-day course of oral Ribavirin 400mg twice daily
Comparator (standard care or generic drug name and dosage)	No Intervention: Usual Care	Active comparator: Clofazimine Oral 100mg twice daily on day 1, then 100mg daily for 2 days. +Standard care	Standard care alone

		Control: standard care alone	
Primary Outcome(s)	Incidence of adverse events (AEs) [Time Frame: Up to 30 days post treatment initiation] Kinetics of viral load in nasopharyngeal swabs [Time Frame: Up to 30 days post treatment initiation]	Clinical alleviation of symptoms [Time Frame: 7 days] Time to complete alleviation of symptoms as defined by NEWS of 0 maintained for 24 hour	Clinical symptoms alleviation [Time Frame: 7 days] Time to complete alleviation of symptoms as defined by NEWS2 of 0 maintained for 24 hours
Sponsor/ lead institution, country (also country of recruitment if different)	Population Health Research Institute, Brazil, Canada, Chile, Colombia, Equador, Egypt, Pakistan, Philippines, Russia, Saudi Arabia, United Arab Emirates	The University of Hong Kong, China	The University of Hong Kong, China

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-12 Ongoing trials *IFN Lambda*

Active substance	IFN Lambda	IFN Lambda	IFN Lambda	IFN Lambda-1A
Trial Identifier/registry ID(s)/contact	NCT04343976 2020P001083/ ClinicalTrials.gov/ Raymond Chung, Massachusetts General Hospital	NCT04534673/ClinicalTrials.gov/ Ohad Etzion, ohadet@clalit.org.il	NCT04388709/ClinicalTrials.gov/ Lynn Bui, lynn.bui@mssm.edu	NCT04354259/ClinicalTrials.gov/ Josh Booth, joshua.booth@uhn.ca
Study design, study phase	Randomized controlled trial, phase 2	Randomized, open-label, 2 arm, pilot trial, phase 2	Randomized controlled trial, phase 2	Randomized controlled trial, phase 2
Recruitment status	Enrolling by invitation	Recruiting	Not yet recruiting	Recruiting
Number of Patients, Disease severity*	20 (> 18 years old), severity not specified	40 (> 18 years old), severity not specified	66 (> 18 years old), severity not specified	140. Cohort A (Ambulatory): 18-70 years old Cohort B (Hospitalized): ≥ 18 years old Mild to moderate
Setting (hospital, ambulatory,..)	Hospital	Hospital	Hospital	Home or hospital
Intervention (generic drug name and dosage)	Pegylated interferon lambda 180 mcg subcutaneous injection	Lambda 180 mcg S.C + standard care	Peginterferon lambda-1a (Lambda) 180mcg subcutaneous injection once	Experimental: Ambulatory Cohort - a single dose of Peginterferon Lambda-1A 180µg SC at baseline (day 0). Experimental: Hospitalized Cohort -a dose of Peginterferon Lambda-1A 180µg SC at baseline and a second dose on day 7.
Comparator (standard care or generic drug name and dosage)	Subcutaneous injection of saline placebo	Standard care	Best supportive care	Placebo Comparator: Ambulatory Cohort - placebo Patients in the arm will be given a single injection of 0.9% sodium chloride (normal saline) solution at baseline (day 0). Placebo Comparator: Hospitalized Cohort - placebo Patients in the arm will be given an injection of 0.9% sodium chloride (normal saline) solution at baseline (day 0) and on day 7
Primary Outcome(s)	Undetectable COVID PCR at day 7.	Viral shedding in days since initial diagnosis [Time Frame: 21 days].	Number of participants with resolution of hypoxia [Time Frame:	Cohort A (Ambulatory) - Proportion swab negative at day 7 (Primary

	Negative COVID PCR testing 7 days after first lambda dose	The duration of viral shedding in days since initial diagnosis, as determined by RT-PCR to COVID-19. Rate of adverse events and severe adverse events [Time Frame: 21 days from entry]. Rate of treatment-emergent and treatment-related severe adverse events (SAEs)	7 days] The clinical improvement as defined as resolution of hypoxia requiring supplemental oxygen to maintain SpO2>92% at 7 days.	efficacy endpoint) [Time Frame: At day 7] Cohort A (Ambulatory) - Treatment-emergent and treatment related serious adverse events (Primary Safety Endpoint) [Time Frame: Day 0 to Day 30 Cohort B (Hospitalized) - Time to viral negativity (Primary Efficacy Endpoint) [Time Frame: Day 0 to day 28] Cohort B (Hospitalized) - treatment-emergent and treatment-related serious adverse events (Primary Safety Endpoint) [Time Frame: Day 0 to Day 30]
Sponsor/ lead institution, country (also country of recruitment if different)	Raymond Chung, Massachusetts General Hospital, USA	Soroka University Medical Center, Israel	Icahn School of Medicine at Mount Sinai, USA	University Health Network, Toronto, Canada

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

5 REFERENCES

1. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019): Cochrane; 2019. Available from: http://www.training.cochrane.org/handbook.

2. DerSimonian R LN. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7:177-88.

3. Balshem H HM, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. Journal of Clinical Epidemiology 2011;64:401-6.

4. Samuel CE. Antiviral actions of interferons. Clin Microbiol Rev. 2001;14(4):778-809.

5. Liu YJ. IPC: professional type 1 interferon-producing cells and plasmacytoid dendritic cell precursors. Annu Rev Immunol. 2005;23:275-306.

6. Schneider WM, Chevillotte MD, Rice CM. Interferon-stimulated genes: a complex web of host defenses. Annu Rev Immunol. 2014;32:513-45.

7. Totura AL, Baric RS. SARS coronavirus pathogenesis: host innate immune responses and viral antagonism of interferon. Curr Opin Virol. 2012;2(3):264-75.

8. Sallard E, Lescure FX, Yazdanpanah Y, Mentre F, Peiffer-Smadja N. Type 1 interferons as a potential treatment against COVID-19. Antiviral Res. 2020;178:104791.

9. Markowitz CE. Interferon-beta: mechanism of action and dosing issues. Neurology. 2007;68(24 Suppl 4):S8-11.

10. Bellingan G, Maksimow M, Howell DC, Stotz M, Beale R, Beatty M, et al. The effect of intravenous interferon-beta-1a (FP-1201) on lung CD73 expression and on acute respiratory distress syndrome mortality: an open-label study. Lancet Respir Med. 2014;2(2):98-107.

11. Zheng F ZY, Zhou Z, et al. SARS-CoV-2 clearance in COVID-19 patients with Novaferon treatment: A randomized, open-label, parallel-group trial. Int J Infect Dis2020. p. 84-91.

12. Wang H MC, Li J, Xu, J Xu, Zhang R, Wang L, et al. , inventorRecombinant human interferon-like proteins2011.

13. Li M, Rao C, Pei D, Wang L, Li Y, Gao K, et al. Novaferon, a novel recombinant protein produced by DNA-shuffling of IFN-α, shows antitumor effect in vitro and in vivo. Cancer Cell Int. 2014;14(1):8.

14. FDA. EXTAVIA (interferon beta-1b) for injection, for subcutaneous use Initial U.S. Approval: 1993 2019 [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125290s067lbl.pdf.

15. Iran CC. ReciGen® (interferon beta-1a) 2020 [Available from: https://www.cinnagen.com/Product.aspx?t=2&l=1&Id=66&f=2#.

16. Zheng F ZY, Zhou Z, et al. A Novel Protein Drug, Novaferon, as the Potential Antiviral Drug for COVID-19: MedRxiv; 2020 [Available from: https://www.medrxiv.org/content/10.1101/2020.04.24.20077735v1.full.pdf.

17. Davoudi-Monfared E, Rahmani H, Khalili H, Hajiabdolbaghi M, Salehi M, Abbasian L, et al. A Randomized Clinical Trial of the Efficacy and Safety of Interferon β-1a in Treatment of Severe COVID-19. Antimicrob Agents Chemother. 2020;64(9).

18. Huang YQ, Tang SQ, Xu XL, Zeng YM, He XQ, Li Y, et al. No Statistically Apparent Difference in Antiviral Effectiveness Observed Among Ribavirin Plus Interferon-Alpha, Lopinavir/Ritonavir Plus Interferon-Alpha, and Ribavirin Plus Lopinavir/Ritonavir Plus Interferon-Alpha in Patients With Mild to Moderate Coronavirus Disease 2019: Results of a Randomized, Open-Labeled Prospective Study. Front Pharmacol. 2020;11:1071.

19. Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020;395(10238):1695-704.

20. Idelsis E-M, Jesus P-E, Yaquelin D-R, Dania V-B, Monica B-R, Lisandra B-R, et al. Effect and safety of combination of interferon alpha-2b and gamma or interferon alpha-2b for negativization of SARS-CoV-2 viral RNA. Preliminary results of a randomized controlled clinical trial. medRxiv. 2020:2020.07.29.20164251.

21. Pan H, Peto R, Karim QA, Alejandria M, Henao-Restrepo AM, García CH, et al. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. medRxiv. 2020:2020.10.15.20209817.

22. Rahmani H, Davoudi-Monfared E, Nourian A, Khalili H, Hajizadeh N, Jalalabadi NZ, et al. Interferon β-1b in treatment of severe COVID-19: A randomized clinical trial. International immunopharmacology. 2020;88:106903.

23. Wang M, Zhao Y, Hu W, Zhao D, Zhang Y, Wang T, et al. Treatment of COVID-19 Patients with Prolonged Post-Symptomatic Viral Shedding with Leflunomide -- a Single-Center, Randomized, Controlled Clinical Trial. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2020.

24. Monk PD, Marsden RJ, Tear VJ, Brookes J, Batten TN, Mankowski M, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet Respiratory Medicine.

25. Jagannathan P, Andrews JR, Bonilla H, Hedlin H, Jacobson KB, Balasubramanian V, et al. Peginterferon Lambda-1a for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial. medRxiv. 2020:2020.11.18.20234161.

26. Khamis F, Al Naabi H, Al Lawati A, Ambusaidi Z, Al Sharji M, Al Barwani U, et al. Randomized controlled open label trial on the use of favipiravir combined with inhaled interferon beta-1b in hospitalized patients with moderate to severe COVID-19 pneumonia. International Journal of Infectious Diseases. 2021;102:538-43.

27. Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol. 2020;92(7):797-806.

28. Taboada M, Rama P, Pita-Romero R, Moreno E, Leal S, Varela M, et al. Pacientes críticos COVID-19 atendidos por anestesiólogos en el Noroeste de España: estudio multicéntrico, prospectivo, observacional. Revista Española de Anestesiología y Reanimación. 2020.

6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

DEPLazio, the Department of Epidemiology of the Regional Health Service Lazio in Rome, Italy is responsible for setting up the search strategy to identify randomised controlled trials (RCTs). DEPLazio performed a search in Medline, PubMed, and Embase, which has been updated weekly from March 2020 (Appendix Table 6-1). DEPLazio searched medRxiv.org (https://www.medrxiv.org/), bioRxiv.org (https://www.bioRxiv.org/), and arXiv.org (https://www.arXiv.org/) for preprints of preliminary reports of randomised trials. The Cochrane Covid-19 Study Register (https://covid-19.cochrane.org/), ClinicalTrials.gov (www.clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) were search in addition. Other sources included journal alerts, contact with researchers, websites such as Imperial College, London School of Hygiene and Tropical Medicine, and Eurosurveillance. We applied no restriction on language of publication.

We included randomised controlled trials (RCTs) comparing any pharmacological intervention against another pharmacological intervention or placebo or standard care (SC), for the treatment of individuals with Covid-19. We excluded studies comparing two dosages of the same pharmacological agent. We did not exclude studies on individuals with a comorbid disorder.

Four authors independently screened the references retrieved by the search, selected the studies, and extracted the data, using a predefined data-extraction sheet. The same reviewers discussed any uncertainty regarding study eligibility and data extraction until consensus was reached; conflicts of opinion were resolved with other members of the review team. Two authors independently assessed the risk of bias of the included studies with the Cochrane tool. Three authors used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, to evaluate the strength of evidence.

The methods described above are part of a living review of pharmacological agents for the treatment of Covid-19 conducted by the Department of Epidemiology of the Regional Health Service Lazio, Italy, to inform national regulatory agencies and clinicians, available at https://www.deplazio.net/farmacicovid. The review is registered on Prospero (CRD42020176914).

Table 6-1 Search strategy to identify randomised controlled studies

Database	URL	Search line / Search terms	Date of search
Pubmed	pubmed.ncbi.nlm.nih.gov	1. (((((((("Coronavirus"[Mesh]) OR (coronavirus*[Title/Abstract] OR coronovirus*[Title/Abstract] OR coronavirinae*[Title/Abstract] OR Coronavirus*[Title/Abstract] OR Coronovirus*[Title/Abstract] OR Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR Huanan[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR 2019nCoV[Title/Abstract] OR nCoV2019[Title/Abstract] OR "nCoV-2019"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR COVID19[Title/Abstract] OR "CORVID-19"[Title/Abstract] OR CORVID19[Title/Abstract] OR "WN-CoV"[Title/Abstract] OR WNCoV[Title/Abstract] OR "HCoV-19"[Title/Abstract] OR HCoV19[Title/Abstract] OR CoV[Title/Abstract] OR "2019 novel*"[Title/Abstract] OR Ncov[Title/Abstract] OR "n-cov"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR SARSCov19[Title/Abstract] OR "SARS-Cov19"[Title/Abstract] OR "SARSCov-19"[Title/Abstract] OR "SARS-Cov-19"[Title/Abstract] OR Ncovor[Title/Abstract] OR Ncorona*[Title/Abstract] OR Ncorono*[Title/Abstract] OR NcovWuhan*[Title/Abstract] OR NcovHubei*[Title/Abstract] OR NcovChina*[Title/Abstract] OR NcovChinese*[Title/Abstract])) OR ((((respiratory*[Title/Abstract] AND (symptom*[Title/Abstract] OR disease*[Title/Abstract] OR illness*[Title/Abstract] OR condition*))[Title/Abstract] OR "seafood market*"[Title/Abstract] OR "food market*")[Title/Abstract] AND (Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR China*[Title/Abstract] OR Chinese*[Title/Abstract] OR Huanan*))[Title/Abstract])) OR ("severe acute respiratory syndrome*")) OR ((corona*[Title/Abstract] OR corono*)[Title/Abstract] AND (virus*[Title/Abstract] OR viral*[Title/Abstract] OR virinae*)[Title/Abstract])) AND (((((((randomized controlled trial [pt]) OR (controlled clinical trial [pt])) OR (randomized [tiab])) OR (placebo [tiab])) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab])) OR (trial [ti]))) NOT (animals [mh] NOT humans [mh]) AND (2019/10/01:2020[dp])	10/12/2020

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	1. exp coronavirus/ 2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. 3. (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw. 4. (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. 5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. 6. "severe acute respiratory syndrome*".ti,ab,kw. 7. or/1-6 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. random*.ab. 11. placebo.ab. 12. clinical trials as topic.sh. 13. random allocation.sh. 14. trial.ti. 15. or/8-14 16. exp animals/ not humans.sh. 17. 15 not 16 18. 7 and 17 19. limit 18 to yr="2019 -Current"	10/12/2020
OVID EMBASE	ovidsp.dc2.ovid.com	1. exp Coronavirinae/ or exp Coronavirus/ 2. exp Coronavirus infection/ 3. ((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) adj4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and (wuhan or china or chinese)) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,kw. 4. or/1-3 5. Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/ 6. (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab. 7. 5 or 6 8. 4 and 7 9. limit 8 to yr="2019 -Current"	10/12/2020

6.2 Search strategy to identify observational studies

As of October 2020, NIPHNO is responsible for setting up the search strategy to identify observational studies. We receive studies that EPPI Centre has screened after searching weekly in Medline and Embase. We supplement these studies with a weekly search in Scopus. The retrieved hits were imported into an Endnote database and combined with generic names of the 17 included COVID-19 drugs.

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search
OVID Medline	Imported from EPPI Centre	1 exp Coronavirus/ 2 exp Coronavirus Infections/ 3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4 (or/1-3) and ((20191* or 202*).dp. or 20190101:20301231.(ep).) 5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. 6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. 7 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. 8 COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os. 9 ("32240632" or "32236488" or "32268021" or "32267941" or "32169616" or "32267649" or "32267499" or "32267344" or "32248853" or "32246156" or "32243118" or "32240583" or "32237674" or "32234725" or "32173381" or "32227595" or "32185863" or "32221979" or "32213260" or "32205350" or "32202721" or "32197097" or "32196032" or "32188729" or "32176889" or "32088947" or "32277065" or "32273472" or "32273444" or "32145185" or "31917786" or "32267384" or "32265186" or "32253187" or "32265567" or "32231286" or "32105468" or "32179788" or "32152361" or "32152148" or "32140676" or "32053580" or "32029604" or "32127714" or "32047315" or "32020111" or "32267950" or "32249952" or "32172715").ui. 10 or/6-9 11 5 or 10	26/10/2020 until 30/11/2020 And from 1/09/2020 until 30/11/2020 for the new compounds Regeneron, Bamlanivimab, Baricitinib, Molnupiravir
OVID EMBASE		1 exp Coronavirus Infections/ 2 exp coronavirinae/ 3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4 or/1-3	26/10/2020 until 30/11/2020 And from 1/09/2020 until 30/11/2020 for the new compounds Regeneron, Bamlanivimab, Baricitinib, Molnupiravir

		5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. 6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. 7 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. 8 6 or 7 9 5 or 8	
Scopus		TITLE-ABS-KEY(((pneumonia OR covid* OR coronavirus* OR "corona virus*" OR ncov* OR 2019-ncov OR sars*) AND Wuhan) OR 2019-ncov OR ncov19 OR ncov-19 OR "2019-novel CoV" OR sars-cov2 OR sars-cov-2 OR sarscov2 OR sarscov-2 OR sars-coronavirus2 OR sars-coronavirus-2 OR "SARS-like coronavirus*" OR coronavirus-19 OR covid19 OR covid-19 OR "covid 2019" OR ((novel OR new OR nouveau) W/1 (CoV OR nCoV OR covid OR coronavirus* OR "corona virus*" OR pandemi*)) OR ((covid OR covid19 OR covid-19) AND pandemic*) OR ((coronavirus* OR "corona virus*") AND pneumonia)) AND ORIG-LOAD-DATE > 20200920[date changes from week to week] AND ORIG-LOAD-DATE < 20200928 [date changes from week to week] AND NOT INDEX(medline)	26/10/2020 until 30/11/2020 And from 1/09/2020 until 30/11/2020 for the new compounds Regeneron, Bamlanivimab, Baricitinib, Molnupiravir

6.3 Search strategy to identify ongoing studies

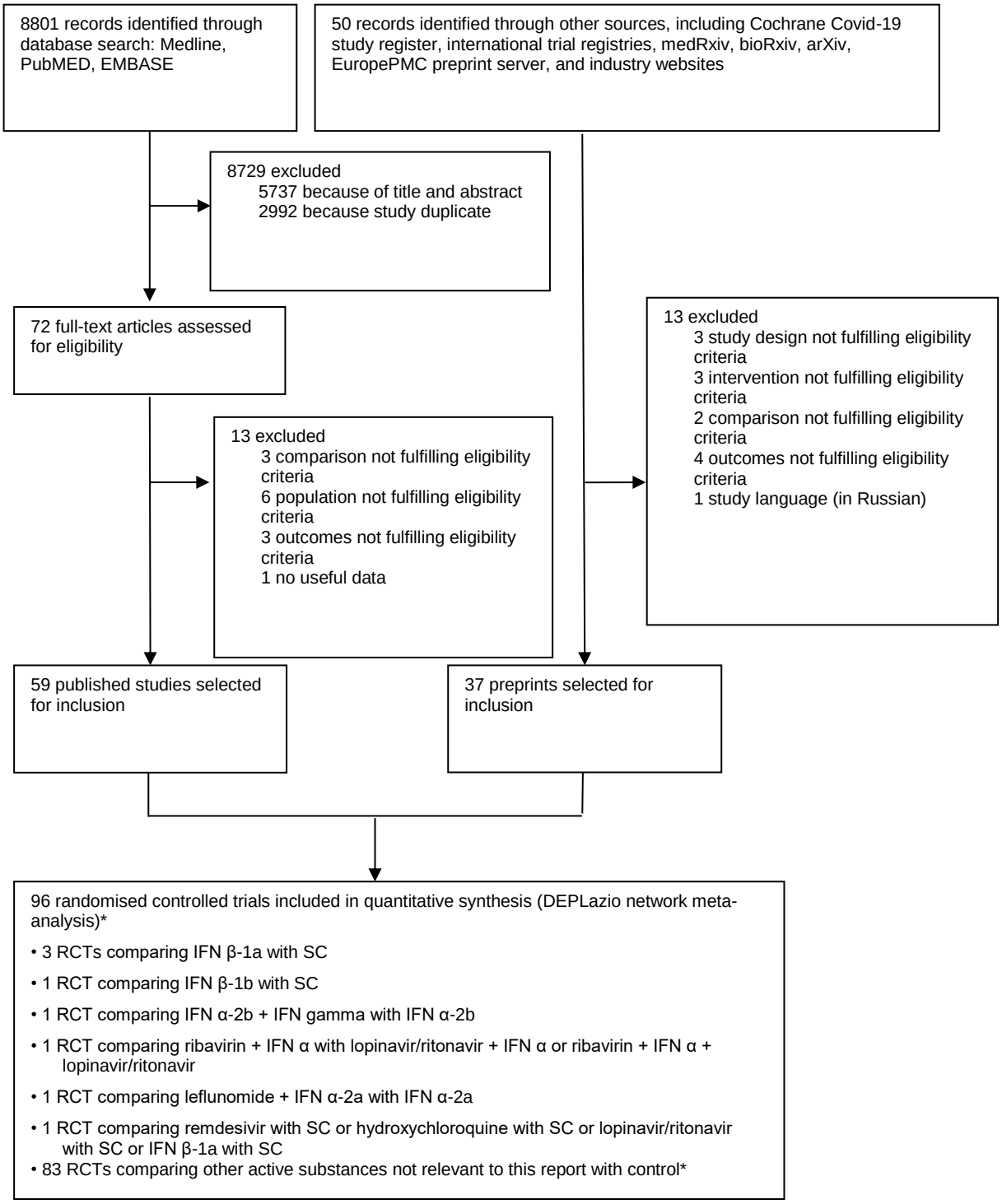
NIPHNO is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and Interferon beta-1a and Novaferon are described in Appendix Table 6-3.

Table 6-3 Search strategy to identify ongoing studies

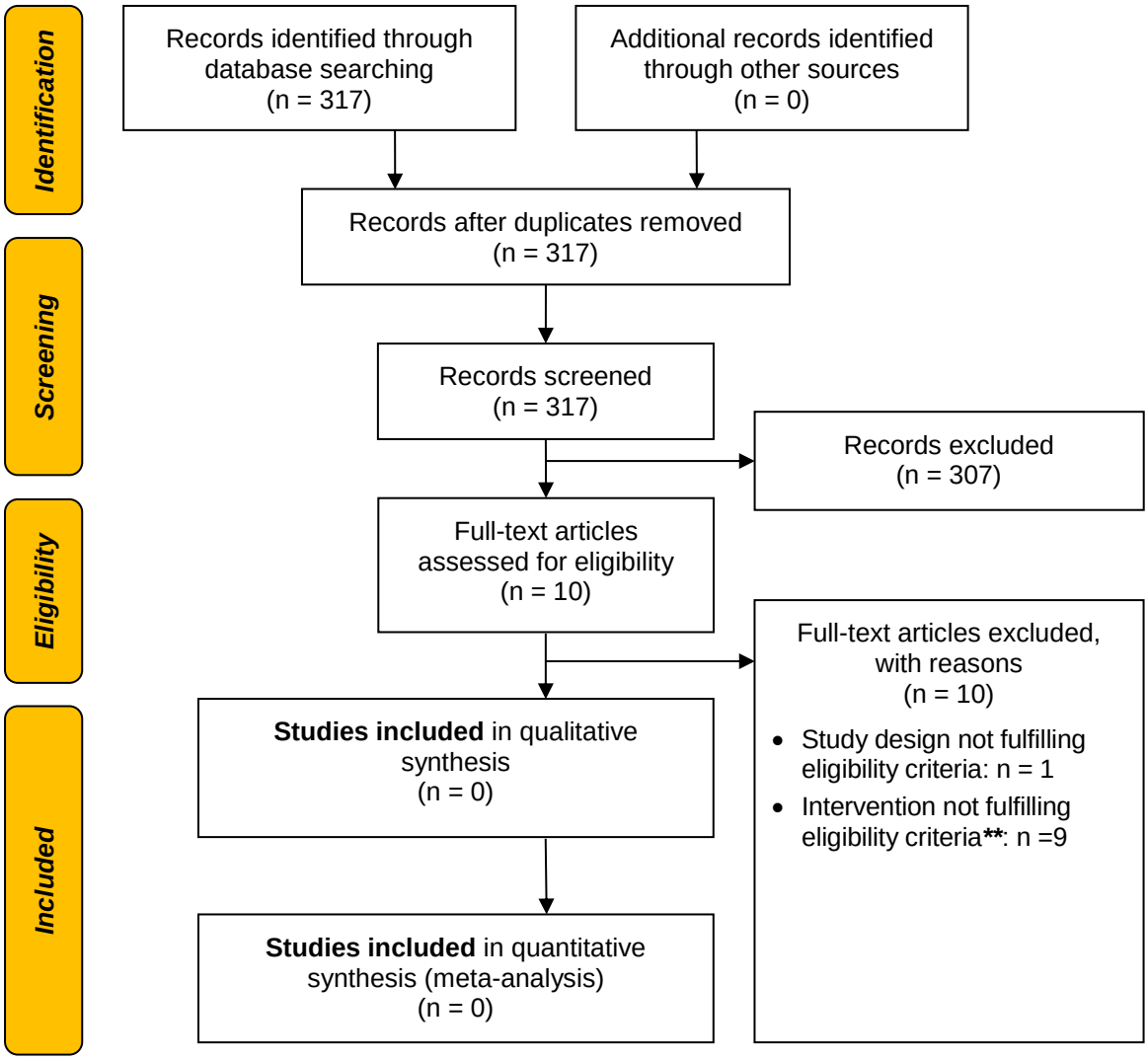
Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	"Basic search mode*" Terms used at Condition or disease: • covid-19 Terms used at "other terms": • Interferon • Novaferon • IFN	28/11/2020	110
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: 1. covid-19 and interferon 2. covid-19 and novaferon 3. SARS-CoV-2 and interferon 4. SARS-CoV-2 and novaferon	28/11/2020	15
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: 1. covid-19 and interferon 2. covid-19 and novaferon 3. SARS-CoV-2 and interferon 4. SARS-CoV-2 and novaferon	28/11/2020	118

***** In Basic Search mode, one term was added to the field "condition or disease" and one term in the field "other terms".

6.4 Flow diagrams



Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs
RCT = randomised controlled trial;
* The selection process was part of an external project, see https://www.deplazio.net/farmacicovid and Prospero ID CRD42020176914.



Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies
****** studies evaluating active substances relevant to other EUNETHTA rolling collaborative reviews