EUnetHTA Joint Action 3 WP4

"Rolling Collaborative Review" of Covid-19 treatments

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

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Major changes from previous version

Chapter, page no.	Major changes from version [1.0]
Effectiveness and Safety evidence from RCTs, pages 10-11	Additional studies included
Ongoing studies, page 11	Additional trials included
Methods, Appendix	The description of the search methods for observational and ongoing studies is expanded: • Search methods are described in Appendix Table 6-1, Table 6-2 and Table 6-3. • Three flow diagrams are added to describe the study selection process of randomized controlled trials (Appendix Figure 6-1); observational studies (Appendix Figure 6-2); and ongoing studies (Appendix Figure 6-3).

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Conflict of interest

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

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TABLE OF CONTENTS

DOCUMENT HISTORY AND CONTRIBUTORS 2
TABLE OF CONTENTS 4
LIST OF TABLES AND FIGURES 4
1 OBJECTIVE 6
2 METHODS 6
2.1 SCOPE 6
2.2 SOURCES OF INFORMATION 8
3 ABOUT THE TREATMENT 10
3.1 MODE OF ACTION 10
3.2 REGULATORY STATUS 10
3.3 LEVEL OF EVIDENCE 10
4 SUMMARY 11
4.1 EFFECTIVENESS AND SAFETY EVIDENCE FROM RCTS 11
4.2 SAFETY EVIDENCE FROM OBSERVATIONAL STUDIES 11
4.3 ONGOING STUDIES 11
4.4 SCIENTIFIC CONCLUSION ABOUT STATUS OF EVIDENCE GENERATION 12
5 REFERENCES 34
6 APPENDIX 36
6.1 SEARCH STRATEGY TO IDENTIFY RANDOMISED CONTROLLED TRIALS 36
6.2 SEARCH STRATEGY TO IDENTIFY OBSERVATIONAL STUDIES 39
6.3 SEARCH STRATEGY TO IDENTIFY ONGOING STUDIES 41
6.4 FLOW DIAGRAMS 42

LIST OF TABLES AND FIGURES

Table 2-1 Scope of the RCR 6
Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of IFN and Novaferon 13
Table 4-2 Ongoing trials 21
Table 6-1 Search strategy to identify randomised controlled studies 37
Table 6-2 Search strategy to identify observational studies 39
Table 6-3 Search strategy to identify ongoing studies 41

Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs 42
Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies for the period 24 August to 27 September 43
Appendix Figure 6-3. Flow diagram depicting the selection process of ongoing studies 44

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	<u>Main outcome:</u> • All-cause Mortality (Survival) <u>Additional Outcomes:</u> Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.
Study design	Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)

2.2 Sources of information

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

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

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

The literature search is conducted in the following databases:

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

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

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

- medRxiv Health Sciences
- bioRxiv Biology

In addition to the sources and strategies described above, registers of ongoing studies are screened. Key conferences and conference proceedings are considered. 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. The process of study selection is depicted in a flow diagram (Appendix Figure 6-3). 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 Appendix **Figure 6-3**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]. Novaferon's non-proprietary name was initially "recombinant cytokine gene-derived protein injection" given by Chinese Pharmacopeia Committee, and the recommended international non-proprietary name (rINN) by WHO is not available yet.

3.3 Level of Evidence

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

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

An Iranian RCT [16] including 92 patients evaluates the effects of IFN β-1a (n=46) compared to standard treatment (n=46). The authors report significantly higher discharge rate and lower mortality rate in the IFN β-1a -group at 14 days. The certainty of the evidence is very low. Another Iranian RCT [17] including 80 patients reports no difference between of IFN β-1b (n=40) compared to standard treatment (n=40) for any of the outcomes evaluated (low certainty of evidence). A Cuban RCT [18] with 63 patients reports no effect of IFN α-2b (n=30) compared to standard treatment (n=33) for all outcomes assessed except for SARS-CoV-2 clearance at 5 days, which was significantly higher in the intervention group (very low certainty of evidence). Two Chinese RCTs [19, 20] combining IFN α (including type α-2a) with ribavirin, Lopinavir / Ritonavir or Leflunomide do not show any effect of IFN α in terms of effectiveness or safety.

One Chinese RCT [11] with three arms including 89 patients has evaluated the effect of Novaferon (n=30), Lopinavir/Ritonavir (n=29) and Novaferon + Lopinavir/Ritonavir (n=30) in COVID-19 patients. The groups treated with Novaferon alone or in combination with Lopinavir/Ritonavir showed significantly higher clearance rates on day 6 than the group treated with Lopinavir/Ritonavir alone, but the certainty on the evidence is very low. No serious adverse events were reported.

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

4.2 Safety evidence from observational studies

We identified no observational studies that met the inclusion criteria. We searched in the electronic databases on the 28th September and exported the retrieved references to Covidence. The use of a retrospective design and small sample size represented the most common reasons for exclusion.

A case series study conducted in China, documented the treatment of 135 hospitalized patients who received traditional Chinese medicine alongside antiviral therapy (Kaletra or interferon), corticosteroids, and antibacterial treatment. We excluded this study as it did not specify the type of interferon that was provided to the patients [21].

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 24 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 4-2).
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): 4 ongoing studies
- IFN β-1a and Novaferon (single agents): 7 ongoing studies
- IFN β-1a and Novaferon (combination therapies): 5 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 effect and safety of IFN β-1a, IFN β-1b, IFN α-2b and Novaferon (Nova) is poor, and any solid conclusion is constrained due to the very low certainty on the findings from the randomized trials. No safety data form observational studies are available. An important number of trials with large populations are ongoing, which might plausibly strengthen the knowledge on these substances for the treatment of people affected by COVID-19.

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

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

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 (14 days)	304 per 1000	87 per 1000	RR 0.29 (0.10 to 0.80)	216 fewer per 1000 (from 274 fewer to 61 fewer)	92	Very low
Number discharged at end of treatment (14 days)	370 per 1000	609 per 1000	RR 1.65 (1.06 to 2.56)	240 more per 1000 (from 22 more to 577 more)	92	Very low
Number with adverse events	22 per 1000	304 per 1000	RR 14.00 (1.92 to 102.13)	283 more per 1000 (from 20 more to 1.000 more)	92	Very low
Duration of ICU admission (days)	8,52 (7,48)	7,71 (8,75)	-	SMD 0.1 lower (0.51 lower to 0.31 higher) in intervention group	92	Very low
Duration of hospitalization (days)	12,25 (7,48)	14,80 (8,45)	-	SMD 0.32 higher (0.09 lower to 0.73 higher) in intervention group	92	Very low

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

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

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 [17]

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 [18]

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 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 [19]

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	611 per 1000	RR 0.77 (0.49 to 1.20)	141 fewer per 1000 (from 312 fewer to 122 more)	68	Low

Progression of COVID-19 disease	63 per 1000	56 per 1000	RR 1.13 (0.17 to 7.53)	7 more per 1000 (from 46 fewer to 363 more)	68	Low
Number of patients with any adverse event	938 per 1000	722 per 1000	RR 1.30 (1.04 to 1.62)	217 more per 1000 (from 29 more to 448 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 [19]

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	-	-	-	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 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 [19]

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 [20]

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	138 per 1000	0 per 1000	RR 0.11 (0.01 to 1.91)	123 fewer per 1000 (from 137 fewer to 126 more)	59	Very low
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 [11].

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	517 per 1000	RR 1.35 (0.89 to 2.06)	181 more per 1.000 (from 57 fewer to 548 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	897 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 [11].

Table 4-2 Ongoing trials

IFN-α, single and in combination

Active substance	**IFN-α**	**IFN α-2b**	**IFN-α2β**	**IFN-α-2b + Hydrochloride**
Sponsor	Peter MacCallum Cancer Centre, Australia	Cadila Healthcare Limited	Tongji Hospital	Tongji Hospital
Trial Identifier	NCT04534725	NCT04480138	NCT04293887	NCT04254874
Phase & Intention	Phase 3. To evaluate several different immune modulating drugs for prevention and treatment of COVID-19 specifically in the cancer population	Phase 2. To evaluate the efficacy and safety of pegylated interferon α-2b in the treatment of adult patients diagnosed with SARS-CoV2 (COVID-19)	Phase1. To evaluate the efficacy and safety of recombinant human interferon α1β in treating patients with new coronavirus infection in Wuhan.	Phase 4. To compare the efficacy of two therapeutic schemes (abidol hydrochloride, abidol hydrochloride combined with interferon atomization) in the treatment of 2019-nCoV viral pneumonia
Study design	Randomized controlled trial	Randomized Controlled Trial	Randomized controlled trial	Prospective/Retrospective, Randomized Controlled Cohort Study
Status of trial	Not yet recruiting	Recruiting	Not recruiting	Recruiting
Duration/End of Study	September 2020 – September 2021	August 11, 2020 – December 15, 2020	March 1, 2020 – May 30, 2020	February 1, 2020 – June 1, 2020
Number of Patients	2 282 (cancer patients ≥ 18 years old)	40 (> 18 years old)	328 (> 18 years old)	100 (≥ 18 years old)
Disease severity	Not yet tested positive	Not specified	Not specified	Mild to severe
Setting	Home or hospital	Hospital	Hospital and home	Hospital
Country	Australia	Mexico	China	China
Intervention 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 Interferonv(PegIFN-α-2b) atomization was added (45ug, add to sterile water 2ml, twice a day) on the basis of group I.
Comparator (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).

Active substance	**IFN-α**	**IFN α-2b**	**IFN-α2β**	**IFN-α-2b + Hydrochloride**
Duration of observation/ Follow-up	3 months	4 weeks	14 days	14 days
Endpoints **Primary Outcomes**	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 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].	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 devices. 6. Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). 7. Death.	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] Compare the average time of lung imaging recovery after 2 weeks of treatment in each group.
Results/Publication	Not provided	Not provided	Not provided	Not provided

Single agents IFN β-1a and Novaferon

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

Active substance	**IFN β-1a**	**IFN β-1a**	**IFN β-1a**	**IFN β-1a**
	total of two weeks. All patients will receive a total dose of 264 mcg under physician control	daily for 10 days or until discharge		syringe. The Ultra device is filled with the contents of two syringes. Patients inhale one dose per day for 14 days.
Comparator (drug name and dosage)	Standard of care: any pharmacological (e.g. antibiotics, etc.) and non-pharmacological (e.g. oxygen, ventilation, etc.) treatments prescribed on clinical grounds	1. Standard care 2. Lopinavir 400 mg + ritonavir 100 mg: by mouth (or nasogastric tube) every 12 hours for 10 days or until discharge 3. Corticosteroid (dexamethasone): administered as an oral (liquid or tablets) or intravenous preparation 6 mg once daily for 10 days or until discharge 4.Hydroxychloroquine by mouth for a total of 10 days	1. No immune modulation (no placebo) 2. Anakinra 3. Tocilizumab 4. Sarilumab	The placebo will be the same formulation as the study medication but without IFN-β1a (i.e. only the excipients of the SNG001 solution) and will be administered once daily via the I-neb or Ultra nebulizer.
Duration of observation/ Follow-up	29 days	Until death, discharge from hospital or 28 days after randomisation (whichever is sooner). Longer-term (up to 10 years) follow-up will be sought through linkage to electronic healthcare records and medical databases.	Duration of hospital stay up to 90 days. Follow-up at 6 months where feasible.	14 days of treatment + the following 14 days (+/- 3 days) after the patient's last dose or when the last dose of study medication would have been administered if dosing was stopped.
Endpoints Primary Outcomes	Time to negative conversion of SARS-CoV-2 nasopharyngeal swab. Time Frame: from baseline to day 29	All-cause mortality at 28 days after randomisation	The number of days alive and not requiring ICU organ support measured at day 21	Change in condition measured using the Ordinal Scale for Clinical Improvement during the dosing period - minimum of 0 (patient is well) to a maximum of 8 (death). Time Frame: day 1 to day 15 daily and on day 28
Results/Publication	Not provided	Not provided	Not provided	Not provided

Single agents IFN β-1a and Novaferon (continued)

Active substance	**IFN β-1a**	**IFN β-1a**	**IFN β-1a**
Sponsor	Synairgen Research Ltd.	National Institute of Allergy and Infectious Diseases (NIAID)	Pontificia Universidad Catolica de Chile
Trial Identifier	NCT04385095	NCT04492475	NCT04552379
Phase & Intention	Phase 2 aiming to determine the safety and efficacy of inhaled SNG001 (IFN-β1a for nebulisation) for the treatment of patients with confirmed SARS-CoV-2 Infection	Phase 3 trial to evaluate the combination of IFN β-1a and remdesivir compared to remdesivir alone.	Phase 3 aiming to ascertain whether IFN β-1a administered to index cases and household contacts of an index case, starting immediately following confirmed exposure will reduce duration of SARS-CoV-2 detectable by PCR in the index cases, and incidence of SARS-CoV-2 detectable by PCR in household contacts.
Study design	Randomised Double-blind Placebo-controlled Trial	Adaptive randomized double-blind placebo-controlled trial	Cluster RCT
Status of trial	Recruiting	Recruiting	Not yet recruiting
Duration/End of Study	March 16, 2020 to May 31, 2021	August 4, 2020 to November 1, 2023	Estimated Study Start Date: September 2020 Estimated Study Completion Date: December 2021
Number of Patients	820 (> 18 years old)	1038 (> 18 years old)	1240 (> 18 years old)
Disease severity	Not specified	Hospitalized patients	Households will be randomised
Setting	Hospital and home	Hospital	Home
Country	United Kingdom	United States	Chile
Intervention 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 (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	Standard of Care; following national guidelines regarding self-isolation and infection prevention

Active substance	**IFN β-1a**	**IFN β-1a**	**IFN β-1a**
		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.	
Duration of observation/ Follow-up	28 days	29 days	29 days
Endpoints **Primary Outcomes**	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]
Results/Publication	Not provided	Not provided	Not provided

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

Active substance	**IFN β-1a + Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine**	**Hydroxychloroquine + Lopinavir / Ritonavir + IFN β-1a or IFN β-1b**	**Lopinavir/ritonavir + IFN β-1a**	**High dose IFN β-1a + Lopinavir /Ritonavir**	**Remdesivir + IFN β-1a**
	Dosage not reported	Arm 2: Hydroxychloroquine + Lopinavir / Ritonavir + IFN β-1b		of 88µg (24,000 IU) on days 1, 3, 6) + Lopinavir/Ritonavir (Kaletra) [IFN β-1a group] (400mg/100 mg twice a day for 10 days	on Day 1, followed by a 100 mg once-daily maintenance dose of Remdesivir while hospitalized for up to a 10-day total course and 44 mcg of IFN β-1aadministered by a 0.5 mL subcutaneous injection on Days 1, 3, 5, and 7 while hospitalized for a total of 4 doses.
Comparator (drug name and dosage)	Lopinavir / Ritonavir + Single Dose of Hydroxychloroquine Dosage not reported	Hydroxychloroquine + Lopinavir / Ritonavir	Local standard of care alone OR local standard of care plus one of: 2. Remdesivir (daily infusion for 10 days) 3. Chloroquine or hydroxychloroquine (two oral loading doses, then orally twice daily for 10 days) 4. Kaletra (orally twice daily for 14 days)	Low dose IFN β-1a (Recigen) (Subcutaneous injections of 44µg (12,000 IU) on days 1, 3, 6) + Lopinavir/Ritonavir (Kaletra) [IFN β-1agroup] (400mg/100 mg twice a day for 10 days	The IFN β-1a placebo contains either 0.5 mL 0.9% normal saline or 0.5 mL sterile water for injection. Remdesivir is also administrated.
Duration of observation/ Follow-up	14 days after randomization	14 days after randomization	Until death or discharge from hospital	14 days after randomization	29 days
Endpoints Primary Outcomes	Time to clinical improvement [Time Frame: From date of randomization until 14 days later]. Improvement of two points on a seven-category ordinal scale (recommended by the World Health Organization: Coronavirus disease (COVID-2019) R&D. Geneva: World Health	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	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:	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

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**
	Organization) or discharge from the hospital, whichever came first.	(COVID-2019) R&D. Geneva: World Health Organization) or discharge from the hospital, whichever came first.		Coronavirus disease (COVID-2019) R&D. Geneva: World Health Organization) or discharge from the hospital, whichever came first.	medical care; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Not hospitalized, no limitations on activities.
Results/Publication	Not provided	Not provided	Not provided	Not provided	Not provided

IFN β-1b, single and in combination

Active substance	**IFN-β**	**IFN β-1b + Clofazimine**	**IFN β-1b + Ribavirin**	**Inhaled IFN β-1b**
Sponsor	Population Health Research Institute	The University of Hong Kong	The University of Hong Kong	Centre Hospitalier Universitaire, Amiens
Trial Identifier	NCT04324463	NCT04465695 UW 20-463	NCT04494399	NCT04469491
Phase & Intention	Phase 3. To assess therapies to reduce the clinical progression of COVID-19	Phase 2. To conduct an open-label randomized controlled trial on a short course of interferon β-1b and clofazimine combination treatment for patients hospitalized for COVID-19 infection.	Phase 2 trial aiming to evaluate the effects of IFN β-1b and ribavirin combination treatment for patients hospitalized for COVID-19 infection.	Phase 2 trial aiming to assess in hospitalized patients with oxygen for COVID 19, the clinical efficacy on oxygen requirements of the addition of inhaled Interferon type I compared to the control arm.
Study design	Randomized controlled trial	RCT	Open-label RCT	RCT
Status of trial	Recruiting	Recruiting	Recruiting	Not yet recruiting
Duration/End of Study	April 21, 2020 – December 31, 2020	July 14, 2020 to September 30, 2021	July 29, 2020 to August 1, 2022	July 2020 to March 2021
Number of Patients	4000 (≥ 18 years old)	81 (>18 years old)	96 (>18 years old)	60 (>18 years old)
Disease severity	Not specified	Not specified	Hospitalized	Hospitalized
Setting	Home or hospital	Hospital	Hospital	Hospital
Country	Brazil, Canada, Chile, Colombia, Equador, Egypt, Pakistan, Philippines, Russia, Saudi Arabia, United Arab Emirates	China	China	France
Intervention 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)	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	Inhaled IFN β-1b (9.6 MUI x2/d for 48 hours, then 9.6 MUI x1/d for 8 to 16 days), in addition to standard care.

	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.			
Comparator (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 Control: standard care alone	Standard care alone	Aerosol (WFI water and routine care (+/- antibiotics; + appropriate O2 support).
Duration of observation/ Follow-up	30 days	14 days	30 days	15 days
Endpoints **Primary Outcomes**	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	Oxygen requirement score at day 15 and variation oxygen requirement score between day 0 and day 15
Results/Publication	Not provided	Not provided	Hung IF, 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 May 30;395(10238):1695-1704.	Not provided

IFN Lambda

Active substance	**IFN Lambda**	**IFN Lambda**	**IFN Lambda**	**IFN Lambda-1A**
Sponsor	Raymond Chung, Massachusetts General Hospital	Soroka University Medical Center	Icahn School of Medicine at Mount Sinai	University Health Network, Toronto
Trial Identifier	NCT04343976 2020P001083	NCT04534673	NCT04388709	NCT04354259
Phase & Intention	Phase 2 trial to assess the efficacy of Pegylated Interferon Lambda (180 mcg) vs. placebo in inducting quantitative PCR negativity at day 7.	Phase 2 trial to compare treatment with IFN Lambda to standard care in patients with COVID-19.	Phase 2 trial aiming to test the safety and effectiveness of an investigational drug peginterferon lambda-1a in treating COVID-19.	Phase 2. To evaluate peginterferon-lambda in ambulatory and hospitalized patients with mild to moderate COVID-19
Study design	Randomized Controlled Trial	Randomized, open-label, 2 arm, pilot trial	Randomized Controlled Trial	Randomized controlled trial
Status of trial	Recruiting	Recruiting	Not yet recruiting	Recruiting
Duration/End of Study	June 22, 2020 - August 2021	August 5, 2020 – December 31, 2021	September 2020 to May 2021	May 13, 2020 – August 1, 2020
Number of Patients	20 (> 18 years old)	40 (> 18 years old)	66 (> 18 years old)	140. Cohort A (Ambulatory): 18-70 years old Cohort B (Hospitalized): ≥ 18 years old
Disease severity	Not specified	Not specified	Not specified	Mild to moderate
Setting	Hospital	Hospital	Hospital	Home or hospital
Country	USA	Israel	USA	Canada
Intervention 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 (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
Duration of observation/ Follow-up	14 days	21 days	7 days	30 days
Endpoints **Primary Outcomes**	Undetectable COVID PCR at day 7. Negative COVID PCR testing 7 days after first lambda dose	Viral shedding in days since initial diagnosis [Time Frame: 21 days]. 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)	Number of participants with resolution of hypoxia [Time Frame: 7 days] The clinical improvement as defined as resolution of hypoxia requiring supplemental oxygen to maintain SpO2>92% at 7 days.	Cohort A (Ambulatory) - Proportion swab negative at day 7 (Primary 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]
Results/Publication	Not provided	Not provided	Not provided	Not provided

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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])	21 September 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"	21 September 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"	21 September 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 15 included COVID-19 drugs.

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search	Hits retrieved
FHI Live COVID-19 Evidence Map	https://www.fhi.no/en/qk/systematic-reviews-hta/map/	Endnote file of hits retrieved in Medline + Embase + Scopus, combined with generic drug names	24 August and 27 September 2020	460
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	24 August and 27 September 2020	
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*	24 August and 27 September 2020	

		or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4 or/1-3 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)	24 August and 27 September 2020	

6.3 Search strategy to identify ongoing studies

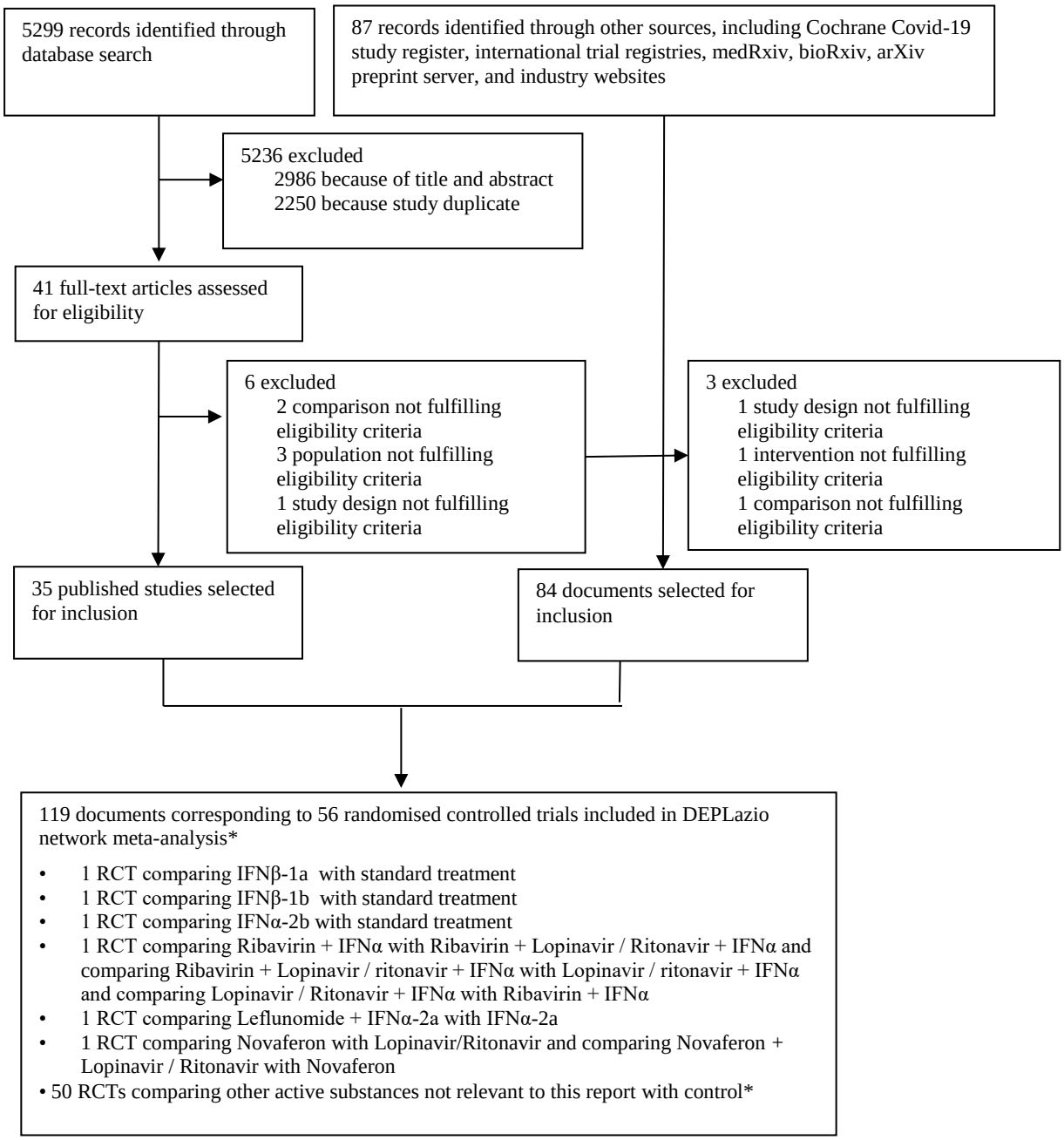
NIPHNO is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and Interferon beta-1a and Novaferon are described in Appendix Table 6-3.

Table 6-3 Search strategy to identify ongoing studies

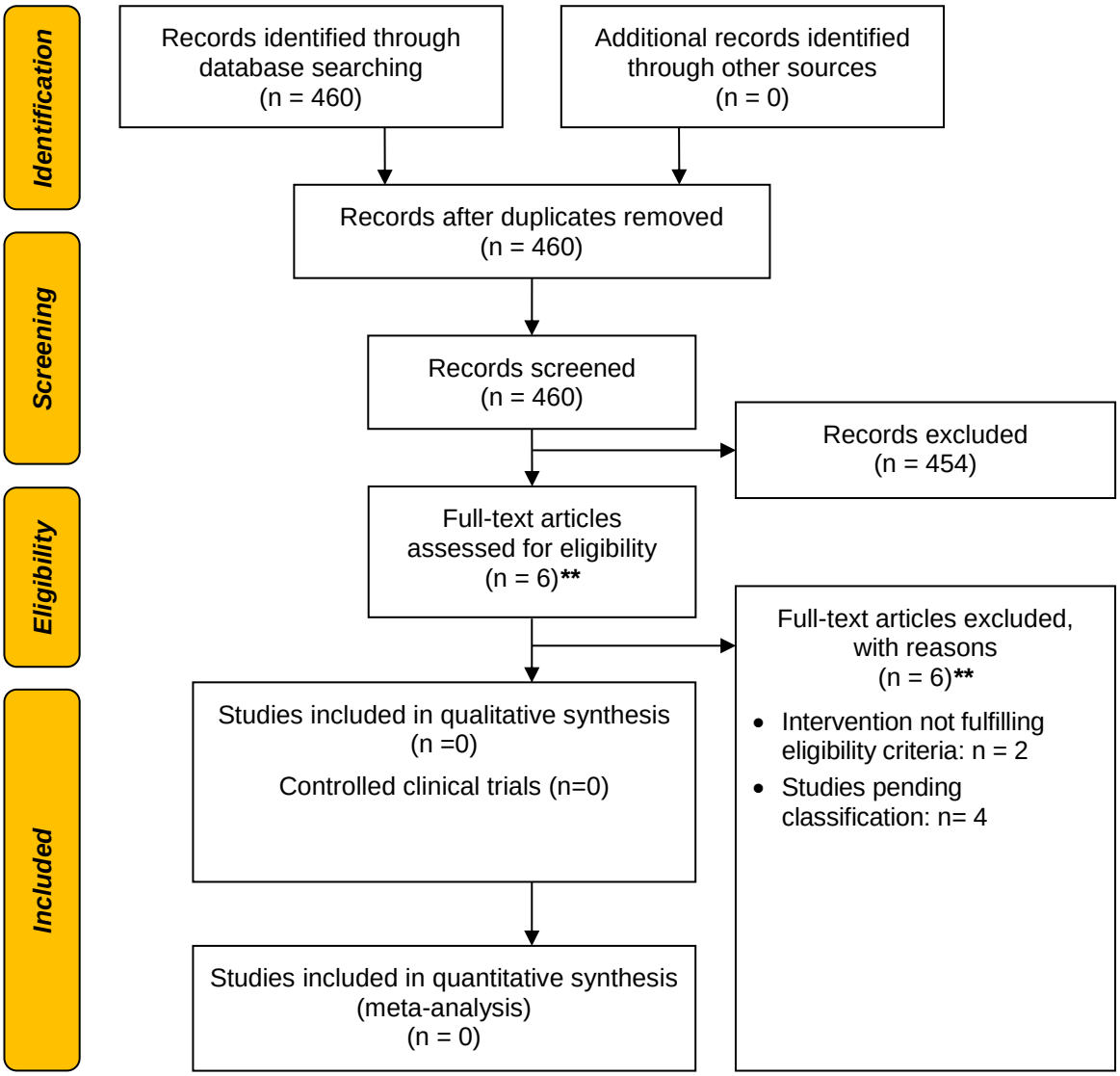
Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	"Basic search mode*" Terms used at Condition or disease: • covid-19 Terms used at "other terms": • Interferon • Novaferon • IFN	28/09/2020	80
ISRCTN	https://www.isrctn.com/	Basic search 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	28/09/2020	8
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	28/09/2020	14

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

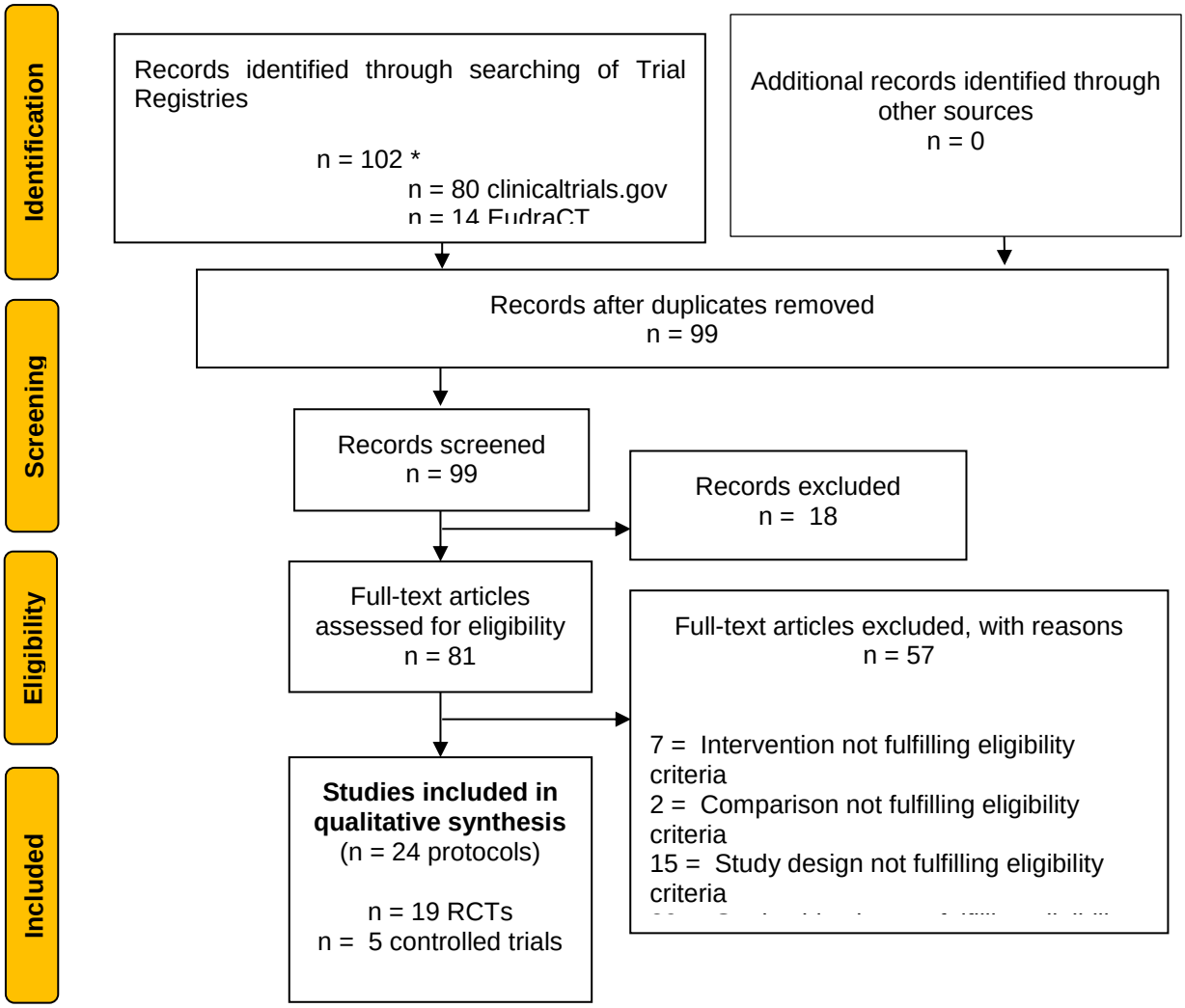
6.4 Flow diagrams



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 for the period 24 August to 27 September
****** studies evaluating active substances relevant to other EUnetHTA rolling collaborative reviews



Appendix Figure 6-3. Flow diagram depicting the selection process of ongoing studies
** 15 added in this update; RCT = randomised controlled trial*