



**A Phase II Multi-Center, Double-Blind,
Randomized and
Controlled Study of the Safety and
Efficacy of Intravenous
Recombinant Human Interferon Beta-1a
in Comparison to
Dexamethasone for the Treatment of
Hospitalized Patients
with COVID-19 Infection**

**Adit Ginde, MD,
Daniel Talmor, MD**

FINAL REPORT

Date: JULY 26, 2022

**59th Medical Wing
Office of the Chief Scientist
1632 Nellis, BLDG. 5406
JBSA Lackland AFB, TX 78236-7517**

DISTRIBUTION A. Approved for public release; distribution is unlimited.

DECLARATION OF INTEREST

The views expressed in this article are those of the authors and do not reflect the official views or policy of the Department of Defense or its Components. The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32 CFR 219 and DODI 3216.02. This work was funded by Project Code Number J917EM01. Authors are military service members, employees, or contractors of the US Government. This work was prepared as part of their official duties. Title 17 USC §105 provides that 'copyright protection under this title is not available for any work of the US Government.' Title 17 USC §101 defines a US Government work as a work prepared by a military service member, employee, or contractor of the US Government as part of that person's official duties.

NOTICE AND SIGNATURE PAGE

Using Government drawings, specifications, or other data included in this document for any purpose other than Government procurement does not in any way obligate the U.S. Government. The fact that the Government formulated or supplied the drawings, specifications, or other data does not license the holder or any other person or corporation or convey any rights or permission to manufacture, use, or sell any patented invention that may relate to them.

Qualified requestors may obtain copies of this report from the Defense Technical Information Center (DTIC) (<http://www.dtic.mil>).

A Phase II Multi-Center, Double-Blind, Randomized and Controlled Study of the Safety and Efficacy of Intravenous Recombinant Human Interferon Beta-1a in Comparison to Dexamethasone for the Treatment of Hospitalized Patients with COVID-19 Infection

Michele F. Tavish

Michele F. Tavish, DAF
Program Analyst
Medical Modernization
59MDW Office of the Chief Scientist



Robert T. Gerhardt, MD, MPH, FACEP, FAEMS
Director, Trauma & Clinical Care Research
59MDW Office of the Chief Scientist

This report is published in the interest of scientific and technical information exchange, and its publication does not constitute the Government's approval or disapproval of its ideas or findings.

REPORT DOCUMENTATION PAGE			<i>Form Approved</i> <i>OMB No. 0704-0188</i>	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering, and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.				
1. REPORT DATE July 12, 2022		2. REPORT TYPE Final Report		3. DATES COVERED 08/2021-04/2022
4. TITLE AND SUBTITLE Study Title: A Phase II Multi-Center, Double-Blind, Randomized and Controlled Study of the Safety and Efficacy of Intravenous Recombinant Human Interferon Beta-1a in Comparison to Dexamethasone for the Treatment of Hospitalized Patients with COVID-19 Infection Subtitle: Human intravenous Interferon Beta-1a Safety and preliminary efficacy in hospitalized subjects with CoronavirUS (HIBISCUS)			5a. CONTRACT NUMBER 47QFWA20C0012	
			5b. GRANT NUMBER ID07200010-301-5.	
			5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Adit Ginde, MD Daniel Talmor, MD			5d. PROJECT NUMBER J917EM01	
			5e. TASK NUMBER 301-5	
			5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) United States Air Force, 59 th Medical Wing (59MDW/ST). 1255 Wilford Hall Loop, Building 4430 Lackland Air Force Base, 78236-9980			8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) Faron Pharmaceuticals Ltd.			10. SPONSOR/MONITOR'S ACRONYM(S) N/A	
			11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Distribution A: Approved for public release; distribution is unlimited.				
13. SUPPLEMENTARY NOTES				
14. ABSTRACT- Viable therapeutic options are extremely limited; therefore, a critical need exists to develop highly effective and rapidly scalable solutions to improve outcomes of severe COVID-19. This proposal directly addresses the programmatic goal of developing therapeutics to treat severe COVID-19. Interferon (IFN) beta-1a (Traumakine [Faron Pharma]) has generated substantial interest in COVID-19 for its known antiviral and immunomodulatory activity. IFN beta-1a plays a key role in host defense against respiratory viruses, preserving endothelial barrier function, and improving alveolar fluid clearance, through CD73-mediated production of adenosine. This phase II, multicenter, blinded, controlled, randomized clinical trial will evaluate IFN beta-1a compared to dexamethasone (control), in addition to standard of care, in patients with severe COVID-19, including pre-ARDS and ARDS. We hypothesize that early administration of intravenous IFN beta-1a will improve clinical status at day 14, compared to dexamethasone, among patients with severe COVID-19. The primary outcome is clinical status at day 14 (where first day of study drug is Day 0) as measured by WHO 9-point ordinal scale: 0 - No detectable infection; 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; 7 - Hospitalized, on mechanical ventilation plus additional organ support: renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO); 8. Death. This project will efficiently yield an answer on the safety and preliminary efficacy of intravenous interferon beta-1a in the early treatment of severe COVID-19.				
15. SUBJECT TERMS- IFN beta-1a; COVID-19; Interferon				
16. SECURITY CLASSIFICATION OF: Unclassified			17. LIMITATION OF ABSTRACT: UU	18. NUMBER OF PAGES 11
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U		
			19b. TELEPHONE NUMBER (include area code)	

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY	2
2.0 INTRODUCTION.....	2
3.0 METHODS, ASSUMPTIONS AND PROCEDURES	2
4.0 MAJOR EVENTS/MILESTONES/SUCCESS	6
5.0 RISK ASSESSMENT	6
5.1 Risk Analysis.....	6
5.2 Technical Challenges	6
6.0 TRANSITION PLAN	7
6.1 Military Relevance	7
6.2 Transition Strategy	7
7.0 RESULTS	7
8.0 CONCLUSION/DISCUSSION	7
9.0 DELIVERABLES	7
9.1 Publications.....	7
9.2 Presentations.....	7
10.0 COST.....	8
11.0 REFERENCES.....	8
TABLES AND FIGURES	10
12.0 List of Symbols, Abbreviations and Acronyms.....	10

1.0 EXECUTIVE SUMMARY

This is a multi-center, double-blind, randomized, and controlled trial of early IV administration of IFN beta-1a compared with dexamethasone in hospitalized patients with COVID-19 infection not requiring high-flow (> 8L/min) oxygen therapy or mechanical ventilation. The primary objective of this study was to demonstrate the safety and tolerability of early intravenous (IV) IFN beta-1a administration in hospitalized patients with COVID-19 infection, compared to dexamethasone; and to investigate the efficacy of IV IFN beta-1a to improve clinical status in hospitalized patients with COVID-19 compared to dexamethasone.

2.0 INTRODUCTION

Viable therapeutic options are extremely limited; therefore, a critical need exists to develop highly effective and rapidly scalable solutions to improve outcomes of severe COVID-19.

This proposal directly addresses the programmatic goal of developing therapeutics to treat severe COVID-19. Interferon (IFN) beta-1a (Traumakine [Faron Pharma]) has generated substantial interest in COVID-19 for its known antiviral and immunomodulatory activity. IFN beta-1a plays a key role in host defense against respiratory viruses, preserving endothelial barrier function, and improving alveolar fluid clearance, through CD73-mediated production of adenosine.

Intravenous recombinant human IFN beta-1a is FDA-approved and widely available for treatment of multiple sclerosis and has been administered in Phase I-III trials for this indication with good tolerability. Pre-clinical and clinical studies suggest that IFN beta-1a is an effective treatment for respiratory viruses (including novel coronaviruses) and ARDS.

Most recently, a pilot Phase II clinical trial showed highly promising results of a related formulation (IFN beta-1b) in improving outcomes in patients with mild-moderate COVID-19. While this formulation does not have the potency and bioavailability needed for treatment of severe COVID-19, these pilot results have generated even greater enthusiasm for IFN beta-1a as a therapy that is highly likely to improve outcomes.

3.0 METHODS, ASSUMPTIONS AND PROCEDURES

Study Preparation:

We will conduct a phase II, multicenter, double-blind, controlled, randomized clinical trial evaluating IFN beta-1a compared to dexamethasone (control), in addition to standard of care, in two subpopulations of patients with severe COVID-19. Our preliminary data indicates a mechanistically grounded interaction between IFN beta-1a and corticosteroids, with IFN beta-1a having the strongest potential for efficacy in the absence of corticosteroids, and potential for safety concerns with co-administration. While data from the open-label/unblinded RECOVERY trial suggests potential benefit from dexamethasone in hospitalized patients with COVID-19, the clinical impact on severe COVID-19 is modest, thus we believe that IFN beta-1a has strong potential for better outcomes with head-to-head comparison. Based on the current evidence and FDA feedback, we do not believe a placebo group would be possible; however, comparison to the active control dexamethasone would be justified and scientifically important. Accordingly, we have designed this Phase II trial to compare IFN beta-1a to dexamethasone to lead toward a definitive answer on intravenous IFN beta-1a in severe COVID-19 patients.

Participants:

We define the target population as adults with severe COVID-19 per the following criteria:

1. Admission to study hospital with acute hypoxemic respiratory failure, requiring supplemental oxygen, and
2. Positive SARS-CoV-2 test by RT-PCR or other molecular test within the past 14 days, and
3. Symptom onset within 7 days prior to hospital arrival.

The source of these patients will be the enrolling hospital ED, hospital ward, or ICUs.

Exclusion criteria to address efficacy, patient safety, and vulnerable populations include:

- 1) Age < 18 years.
- 2) Unable to randomize within 24 hours of meeting inclusion criteria.
- 3) Supplemental high-flow (>8L/min) oxygen therapy or mechanical ventilation
- Known hypersensitivity to natural or recombinant IFN beta or to any of the excipients.
- 4) Use of systemic corticosteroid therapy within seven days of study enrollment.
- 5) Known hypersensitivity to dexamethasone.
- 6) Active or history of systemic fungal infections.
- 7) Uncontrolled hyperglycemia or DKA.
- 8) Continuous home oxygen use for chronic cardiopulmonary disease if patient not mechanically ventilated at study entry.
- 9) Home assisted ventilation except for CPAP/BIPAP used only for sleep-disordered breathing.
- 10) Participation in concurrent interventional trial with treatment or outcomes that could impact interpretation of results for this trial.
- 11) Decision to withhold life-sustaining treatment (Exception: A patient will not be excluded if all supportive care is still being received except for attempts at resuscitation from cardiac arrest);
- 12) Moribund patient not expected to survive 24 hours.
- 13) Prisoner.
- 14) Pregnancy.
- 15) Inability to obtain informed consent

Randomization:

Eligible participants will be randomized on a 1:1 basis to IFN beta-1a or dexamethasone through a centralized, web-based platform in completed in permuted blocks of varying size and stratified by site. Each subject will receive a computer-generated study ID number, which will be provided to the pharmacy who will provide the appropriate study medication. The participant, treating clinicians, and study personnel will all remain blinded to group assignment until after the database is locked and blinded analysis is completed.

Intervention:

Participants randomized to the intervention group will receive once daily doses of 10 mcg of IFN beta-1a; the control group will receive once daily doses of 6 mg of dexamethasone—both will be administered for 6 days. Study medication (IFN beta-1a will be provided by Faron Pharmaceuticals Ltd (Turku, Finland). This study medication is approved under an existing FDA IND 149849 for this trial, as well as utilizing a cross-reference to an existing IND 114392 for FP-1201-lyo in non-COVID ARDS. The first dose will be given within 12 hours of randomization and the injection should be given at the same time each day \pm 2 hours as allowed by the patient's condition.

Systemic corticosteroids treatment at screening is an exclusion criterion in the study. Specific medical conditions requiring immediate corticosteroids treatment are specified in the protocol and once diagnosed, should be treated with corticosteroids and discontinued from IFN beta-

1a/dexamethasone/placebo treatment (subjects will continue for follow up and study assessments). From study Day 7 onward, the treating physician may use corticosteroids if deemed necessary for the study subject's clinical condition.

Study Procedures:

We will recruit patients who test positive for COVID-19 and are in the study hospital's emergency department, hospital ward, or ICUs. We will access our own hospital's testing logs and provider referrals for screening. We will approach eligible patients or their legally authorized representative for prospective informed consent using a 'no-touch' consent process that minimizes risk to research staff and preserves limited PPE, while still adhering to federal/FDA regulations on written informed consent in clinical research. Research personnel will conduct study specific assessments on Day 0, Days 1-28, Day 60, and Day 90 for focused data collection; otherwise clinical routine assessments will be utilized for safety and efficacy assessments. Additional biospecimens will be collected for research purposes.

Outcomes:

The primary outcome is clinical status at day 14 (where first day of study drug is Day 0) as measured by WHO 9-point ordinal scale: 0 - No detectable infection; 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; 7 - Hospitalized, on mechanical ventilation plus additional organ support: renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO); 8. Death.

Secondary outcomes include:

Clinical Endpoints

- Ventilator-free days to Day 28
- Clinical status at day 28 as measured by WHO 9-point ordinal scale
- In-hospital mortality at day 28 and day 90
- ICU-free days to day 28
- Hospital length of stay among survivors to day 90

Physiological Endpoints

- Development and severity of ARDS to day 7
- Vasopressor-free days to day 28
- Renal replacement-free days to day 28
- Duration of mechanical ventilation to day 28
- Oxygenation-free days to day 28
- Incidence of new mechanical ventilation to day 28
- Sequential organ failure assessment (SOFA) score at day 7
- Fever-free days to day 28

Safety Endpoints

- In-hospital serious adverse events to day 14
- In-hospital adverse events possibly related to intervention to day 14
- Serious Adverse Events to day 90
- Discontinuation of study drug infusion

Exploratory Endpoints (days 0, 3, and 7, while hospitalized)

- Qualitative and quantitative PCR for SARS-CoV-2 in OP or NP swab

- Inflammatory cytokine levels in blood
- Interferon beta levels in blood
- Qualitative and quantitative PCR for SARS-CoV-2 in blood

4.0 MAJOR EVENTS/MILESTONES/SUCCESS

In preparation for the execution of this project,

- Kick Off Meeting – 7/21 (Site Initiation Visit)
- IRB/IACUC Approval – 05/21
- All experimental procedures completed – 04/2022 (final visit date for last subject enrolled)
- Data Analysis – N/A
- Poster presentation – provide location and date: N/A
- Manuscript submitted to – name of journal and date: N/A
- Dissemination of Results – N/A

5.0 RISK ASSESSMENT

5.1 Risk Analysis:

1. We launched in Nov 2021, and Omicron started in late Dec/early Jan. Omicron is effectively a completely different disease than Delta or the prior variant.
2. Omicron caused a surge in cases but dramatically lowered the hypoxic cases, the number of hospital admissions, and ALI/ARDS cases
3. From late Jan 2022 through now, the number of COVID Omicron cases has continued to drop dramatically. In effect, despite looking to expand enrollment nationally and internationally, the cases don't exist and have affected enrollment in other large companies as well for therapies (GSK, Pfizer,J&J) which have had to stop some of their trials
4. Adding to it, the variant shift resulted in a delay of arrival to the hospital by patients (they were coming w/in 7 days earlier in the pandemic, which is in our inclusion criteria) and were/are now coming at a mean of 9-10 days requiring us to exclude them
5. Finally, several clinical teams/sites shifted hard in Nov and Dec to giving steroids early and for less severe hypoxic cases (even when the data does not support it) leaving even fewer cases to enroll for this trial on top of the above issues.

Due to these confounding factors, it was decided by the PIs, DSMB and 59MDW to close the study.

5.2 Technical Challenges

1. We launched in Nov 2021, and Omicron started in late Dec/early Jan. Omicron is effectively a completely different disease than Delta or the prior variant.
2. Omicron caused a surge in cases but dramatically lowered the hypoxic cases, the number of hospital admissions, and ALI/ARDS cases
3. From late Jan 2022 through now, the number of COVID Omicron cases has continued to drop dramatically. In effect, despite looking to expand enrollment nationally and internationally, the cases don't exist and have affected enrollment in other large companies as well for therapies (GSK, Pfizer,J&J) which have had to stop some of their trials

4. Adding to it, the variant shift resulted in a delay of arrival to the hospital by patients (they were coming w/in 7 days earlier in the pandemic, which is in our inclusion criteria) and were/are now coming at a mean of 9-10 days requiring us to exclude them

5. Finally, several clinical teams/sites shifted hard in Nov and Dec to giving steroids early and for less severe hypoxic cases (even when the data does not support it) leaving even fewer cases to enroll for this trial on top of the above issues.

6.0 TRANSITION PLAN

6.1 Military Relevance

The U.S. military is at significant risk for COVID-19 infections and related impacts on combat readiness. Early in the pandemic, there was significant cancellation of domestic travel and major military exercises (Military Times 25 MAR 2020). These limitations directly impacted deployments in Syria, Iraq, and Afghanistan, as well as strategic exercises in the Pacific and European regions. The DoD implemented Health Protection Condition (HPCON) Charlie and strict limitations on access to military installations to mitigate risks. As of 30 NOV 2020, travel restrictions are still in place at 121 of 231 DoD installations, including FT Bragg, Offutt AFB, and FT Hood. The U.S. Army has deployed field hospitals to assist with civilian efforts, and the U.S. Navy deployed two hospital ships (Defense.gov 25 MAR 2020). Since the start of the pandemic, the DoD has mobilized over 7,000 doctors, nurses, and medical technicians while the MHS has shifted its research priorities to combat the coronavirus. Despite the interventions, the DoD has reported 86,007 service member, 22,553 civilian, 13,202 dependent, and 7,838 contractor COVID-19 cases, leading to 2,008 hospitalizations and 138 deaths as of December 7, 2020. If proven effective, repurposed medications offer substantial advantage to allow for rapid scalability and deployment in the military and civilian context. Further, lopinavir/ritonavir is a well-tolerated oral therapeutic capable of administration outside of the hospital setting. This is a significant advantage for the U.S. military in both CONUS (e.g., MTFs and base clinics) and OCONUS operations. In addition, non-COVID ARDS is high threat to combat casualty care patients. If non-COVID ARDS patients need to be enrolled as a contingency, evaluating this drug as a therapy for non-COVID ARDS is highly relevant to the DoD's combat casualty care mission.

6.2 Transition Strategy

No transition plan due to study closing early.

7.0 RESULTS

N/A- study closed early

8.0 CONCLUSION/DISCUSSION

N/A -study closed early

9.0 DELIVERABLES

9.1 Publications: N/A- study closed early

9.2 Presentations: N/A-study closed early

10.0 COST

The Not to Exceed (“NTE”) funding for this Task Order is \$4,000,045.84, including taxes, fixed prices for deliverables, and reimbursable expenses. The NTE funding is based upon the fixed labor funding of \$509,501.82, plus reimbursable expenses for Supplies (\$5,570.00), Other Direct Costs (\$3,484,974.02). Any costs or expenses Subcontractor incurs that exceed the NTE funding specified above will be at Subcontractor’s risk.

The amount of funds obligated under this task order is \$4,000,045.84.

11.0 REFERENCES

1. Del Rio C, Malani PN. COVID-19-New Insights on a Rapidly Changing Epidemic. JAMA 2020.
2. Fauci AS, Lane HC, Redfield RR. Covid-19 - Navigating the Uncharted. N Engl J Med 2020;
3. John Hopkins Coronavirus Resource Center <https://coronavirus.jhu.edu>. Accessed 1 Feb 2021
4. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, Azman AS, Reich NG, Lessler J. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med. 2020 May 5;172(9):577-582. doi: 10.7326/M20-0504. Epub 2020 Mar 10. PMID: 32150748.
5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Mar 17;323(11):1061-1069. doi: 10.1001/jama.2020.1585. PMID: 32031570.
6. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708-1720. doi: 10.1056/NEJMoa2002032. Epub 2020 Feb 28. PMID: 32109013
7. Hung IF, Lung KC, Tso EY, 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. doi: 10.1016/S0140-6736(20)31042-4. Epub 2020 May 10. PMID: 324017158
8. National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, Ginde AA, Brower RG, Caterino JM, Finck L, Banner-Goodspeed VM, Grissom CK, Hayden D, Hough CL, Hyzy RC, Khan A, Levitt JE, Park PK, Ringwood N, Rivers EP, Self WH, Shapiro NI, Thompson BT, Yealy DM, Talmor D. Early High-Dose Vitamin D3 for Critically Ill, Vitamin D-Deficient Patients. N Engl J Med. 2019 Dec 26;381(26):2529-2540. doi: 10.1056/NEJMoa1911124. Epub 2019 Dec 11. PMID: 31826336
9. Beitler JR, Sarge T, Banner-Goodspeed VM, Gong MN, Cook D, Novack V, Loring SH, Talmor D; EPVent-2 Study Group. Effect of Titrating Positive End-Expiratory Pressure (PEEP) With an Esophageal Pressure-Guided Strategy vs an Empirical High PEEP-Fio2 Strategy on Death and Days Free From Mechanical Ventilation Among Patients With

- Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *JAMA*. 2019 Mar 5;321(9):846-857. doi: 10.1001/jama.2019.0555. PMID: 30776290
10. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med*. 2020 Jul 17; NEJMoa2021436. doi: 10.1056/NEJMoa2021436. PMID: 32678530.
 11. National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, Moss M, Huang DT, Brower RG, Ferguson ND, Ginde AA, Gong MN, Grissom CK, Gundel S, Hayden D, Hite RD, Hou PC, Hough CL, Iwashyna TJ, Khan A, Liu KD, Talmor D, Thompson BT, Ulysse CA, Yealy DM, Angus DC. Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome. *N Engl J Med*. 2019 May 23;380(21):1997-2008. doi: 10.1056/NEJMoa1901686. Epub 2019 May 19
 12. PETAL Network, Self W, et al. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. *JAMA* 2020. PMID: 33165621 PMCID: PMC7653542 DOI: [10.1001/jama.2020.22240](https://doi.org/10.1001/jama.2020.22240)

FIGURES AND TABLES: None

12.0 LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

ADA Anti-Drug Antibodies
AE Adverse Event
AEP Acute Eosinophilic Pneumonia
AKI Acute Kidney Injury
ALI Acute Lung Injury
ARDS Acute Respiratory Distress Syndrome
BIPAP Bilevel Positive Airway Pressure
BP Blood Pressure
CBC Complete Blood Count
CD73 Cluster of differentiation 73
CI Confidence Interval
CPAP Continuous Positive Airway Pressure
CRA Clinical Research Associate (Monitor)
CT Computerised Tomography
D Day (as in treatment day)
DNR Do Not Resuscitate
ECG Electrocardiogram
ECOG Eastern Cooperative Oncology Group
ECMO Extracorporeal membrane oxygenation
e-CRF Electronic Case Report Form
FAS Full Analysis Set
FU Follow-up
HR Heart Rate
HSP Hypersensitivity Pneumonitis
ICD Informed Consent Document
ICH International Conference on Harmonisation
ICU Intensive Care Unit
IDMC Independent Data Monitoring Committee
IEC Independent Ethics Committee
IFN Interferon
IRB
IMP
Institutional Review Board
Investigational Medicinal Product
IV Intravenous
IWRS Interactive Web-Response System
JAK-STAT Janus kinase-signal transducer and activator of transcription
MERS Middle East Respiratory Syndrome
MIU Million International Units
MOF Multiple Organ Failure
MM Medical Monitor

MxA Myxovirus resistance protein A
NOAEL No Observed Adverse-Effect Level
OSCI WHO ordinal scale for clinical improvement
OTD Optimum Tolerated Dose
PBMC Peripheral Blood Mononuclear Cells
PCR Polymerase Chain Reaction
PerLR Personal Legal Representative
PD Pharmacodynamics
PIM Potential Inflammatory Marker
PPS Per-Protocol Set
PrfLR Professional Legal Representative
RRT Renal Replacement Therapy
SAE Serious Adverse Event
SAP Statistical Analysis Plan
SD Standard Deviation
SUSAR Suspected Unexpected Serious Adverse Reaction
TEAE Treatment-Emergent Adverse Event
WBC White Blood Cells