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

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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

Study code: HIBISCUS (Human intravenous Interferon Beta-Ia Safety and preliminary efficacy in hospitalized subjects with CoronavirUS)

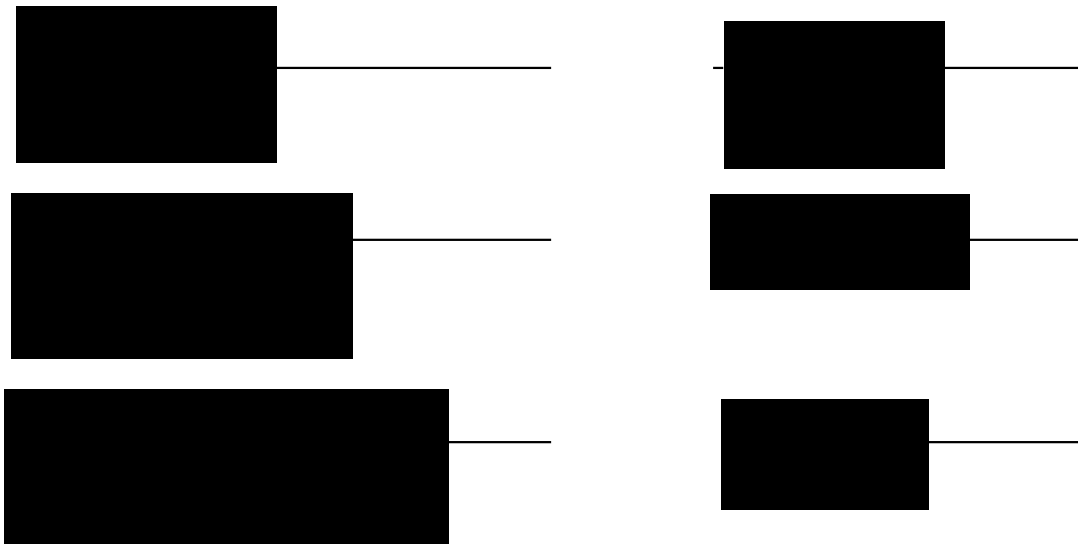
Phase II study

STATISTICAL ANALYSIS PLAN

Signatures:

Statistical Analysis Plan was prepared by:

Statistical Analysis Plan was reviewed/approved by:



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1 Abbreviations

Describe all the abbreviations used in the statistical analysis plan. E.g.

AE	Adverse event
ANOVA	Analysis of variance
CD73	Cluster of differentiation 73
IV	Intravenous
IFN	Interferon
MxA	Myxovirus resistance protein A
PIM	Potential inflammatory marker
PT	Preferred term
SOC	System organ class
TEAE	Treatment-Emergent Adverse Events

2 Early termination of the study

The study was terminated by a sponsors' decision due to changes in the pandemic resulting in difficulties recruiting eligible patients. There were only five patients enrolled and dosed at the time of termination.

3 Study objective(s)

The primary objective of this study was to demonstrate the safety and tolerability of early 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.

The secondary objectives of this study were to assess the immunogenicity of IFN beta-1a and to investigate the efficacy of IV IFN beta-1a on clinical outcomes in hospitalized patients with COVID-19 compared to dexamethasone.

The exploratory objectives of this study were to investigate the efficacy of IV IFN beta-1a on clinical outcomes in hospitalized patients with COVID-19 compared to dexamethasone, to measure the pharmacodynamic (PD) effects of IFN beta-1a (MxA and CD73), to measure IFN beta levels during the treatment, to evaluate potential inflammatory markers (PIMs) response to treatment, and to evaluate genetic susceptibility to IFN beta-1a treatment.

4 Design and type of the study

This was a multicentre Phase II, double-blind, randomized and dexamethasone controlled, study of the safety and preliminary efficacy of IV IFN beta-1a compared with dexamethasone in adult patients diagnosed with COVID-19 needing hospitalization, but not invasive mechanical ventilation or high flow/pressurized supplemental oxygen. The primary endpoint safety and tolerability of IV IFN beta-1a, and primary efficacy endpoint is WHO ordinal scale for clinical improvement (WHO

OSCI) score at D14. Both treatment groups received standard care according to current treatment guidelines. If the patient was subjected for systemic (oral or intravenous) glucocorticoids during the study days D1-D6, the IFN IMP is discontinued, and the patient continued in all follow-up study assessments.

The study population consisted of patients that came into the emergency department for a deteriorated condition due to a suspected or already confirmed SARS-CoV2 infection during the previous 7 days. Approximately 140 subjects were planned to be recruited.

Following randomization, patients were treated daily with IFN beta-1a 10 µg or dexamethasone as an IV bolus for 6 days and undergone daily assessments while hospitalized. The main analysis and reporting were meant to use D14, D28 and D90 data. Final follow-up occurred at D90 by phone or through medical records. During the long-term follow-up periods patient care will follow normal hospital procedures, as appropriate.

5 Sample size considerations

140 patients were to be randomised to active and dexamethasone with 1:1 ratio. Conditional power re-assessment was planned to be conducted at interim analysis after 70 patients have been enrolled and followed up for the primary efficacy endpoint variable.

Sample size calculations were performed and documented earlier, see Appendix A.

6 General statistical considerations

No formal statistical hypotheses are set to be analysed due the early termination of the study with only 5 recruited subjects.

Collected data will be listed and presented descriptively only. Following summary tables will be presented in support to patient listings:

- Study termination and primary reason for discontinuation
- Patient disposition
- Demographic characteristics
- Study drug exposure
- Summary of Treatment-Emergent Adverse Events (TEAEs)
- Deaths

Summary tables regarding adverse events (AEs) will be presented at least by system organ class (SOC), preferred term (PT) and severity including number of patients and events for all TEAEs, severe TEAEs, serious TEAEs, drug-related TEAEs, serious drug-related TEAEs and TEAEs leading to study drug discontinuation.

Based on the data from only 5 individual subjects some of the tables may be left out from the final table package due the sparsity of the table to be meaningful to produce, for example, deaths will not be tabulated if all study participants are alive.

7 Hardware and software

Tables and patient data listings are produced with SAS® 9.4 TS1M6 for Windows (SAS Institute Inc., Cary, NC, USA).

8 References

1. HIBISCUS Study Protocol, version 4.0 (27th September 2021), Faron Pharmaceuticals Ltd.

9 Appendices

A. HIBISCUS updated sample size calculation, final version (1st April 2021).

9.1 Data listing plan

Listing 1 Demographics

Listing 2 Disposition

Listing 3 Termination

Listing 4 Deaths

Listing 5 Adverse events

Listing 6 Exposure

Listing 7 Deviations

Listing 8 Symptoms

Listing 9 Concomitant medications

Listing 10 Medical history

Listing 11 Questionnaires

Listing 12 CD73

Listing 13 Anti-drug antibodies

Listing 14 ARDS

Listing 15 Acute kidney injury

Listing 16 New mechanical ventilation

Listing 17.1 Labs - Chemistry

Listing 17.2 Labs - Hematology

Listing 17.3 Labs - Interferon beta

Listing 17.4 Labs - Myxovirus resistance protein A

Listing 17.5 Labs - Pregnancy

Listing 18 Physical examination

Listing 19 Pharmacogenetics

Listing 20 Scans

Listing 21 Vital signs

9.2 Tabulation plan

1 Demographic Tables	*Table 1.1 Demographics*
	Table 1.2 Disposition
	Table 1.3 Termination
	Table 1.4 Deaths
2 Safety Tables	*Table 2.1 Adverse events*
	Table 2.2 Exposure