# Document Coversheet

Study Title: Phase 1/2A Study of Rintatolimod and IFN alpha Regimen in Cancer Patients with Mild or Moderate COVID-19 Infection

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## PROTOCOL TITLE:

**Phase 1/2A Study of Rintatolimod and IFN alpha Regimen in Cancer Patients with COVID-19**

## PROTOCOL NUMBER:

I-659920

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**Confidentiality Statement**

| | |
|---|---|
| µg | microgram |
| µL | microliter |
| 5-FU | 5-fluorouracil |
| ACE | angiotensin-converting-enzyme |
| AE | adverse events |
| α | alpha |
| αDC | alpha Dendritic Cell |
| ALT | Alanine transaminase |
| ANA | antinuclear antibodies |
| ANC | absolute neutrophil count |
| AST | Aspartate transaminase |
| ARDS | Acute respiratory distress syndrome |
| β | beta |
| BUN | blood urea nitrogen |
| CBER | Center for Biologics Evaluation and Research |
| cc | cubic centimeter |
| CD3 | cluster of differentiation 3 |
| °C | degrees Celsius |
| CKM | chemokine modulatory |
| Cl | chloride |
| cm | centimeter |
| CO2 | carbon dioxide |
| COX2 | Cyclooxygenase-2 |
| CRC | colorectal cancer |
| CRCLM | CRC liver metastasis |
| CRCM | metastatic colorectal cancer |
| CRS | Clinical Risk Score |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| dL | deciliter |
| DLT | Dose Limiting Toxicity |
| DSMC | Data Safety Monitoring Committee |
| (ds)RNA | Double-stranded RNA |
| ECOG | Eastern Cooperative Oncology Group |
| EKG | Electrocardiography |
| °F | degrees Fahrenheit |
| FDA | F |
| g | gram |
| γ | gamma |
| GI | gastrointestinal |
| GMP | good Manufacturing Practices |
| HCG | Human Chorionic Gonadotropin |
| HDI | High Dose Interferon |

| | |
|---|---|
| HPRT | hypoxanthine phosphoribosyl transferase |
| ICH | immunohistochemistry |
| IFN | interferon |
| IL-2 | interleukin-2 |
| im | intramuscular |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| ISH | in situ hybridization |
| IU | International Units |
| IV | intravenous |
| kg | kilogram |
| LPS | lipopolysaccharide |
| m2 | meters squared |
| mg | milligram |
| min | minute |
| mL | milliliter |
| MRI | Magnetic Resonance |
| mRNA | Messenger RNA |
| NCI | National Cancer Institute |
| ng | nanogram |
| NSAID | non-steroidal anti-inflammatory drug |
| PET | Positron emission tomography |
| PGE2 | prostaglandin E2 |
| po | by oral route of administration |
| RPCI | Roswell Park Cancer Institute |
| RP2D | recommended Phase 2 dose |
| SAE | severe adverse events |
| SGOT | Serum Glutamic Oxaloacetic Transaminase |
| SGPT | Serum Glutamic Pyruvate Transaminase |
| SOC | standard of care |
| ssRNA | single-stranded RNA |
| Teff | effector T cells |
| TLR | toll-like receptor |
| Treg | regulatory T cells |
| U | unit |
| ULN | upper limit of normal |
| UPCI | University of Pittsburgh Cancer Institute |

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# 1 STUDY OBJECTIVES

## 1.1 Primary Objectives

- To determine the safety of the combination of IV. rintatolimod administered with or without IV IFNα (INTRON® A) in patients with cancer with COVID-19.
- Determine the kinetics of viral load in nasopharyngeal swabs in the course of treatment and Days 7 and 14.

## 1.2 Secondary Objectives

- To assess the efficacy of the treatment combination in patients with cancer with COVID-19.
- Determine the kinetics of viral load in the peripheral blood in the course of treatment and Days 7 and 14.
- Determine the kinetics of changes of the immune subsets and circulating inflammatory mediators (including CRP, cytokines, chemokines, interferons) in peripheral blood in the course of treatment and Days 7 and 14.
- Determine the induction of known mediators of antiviral immunity that include (myxovirus resistance gene, MxA; protein Kinase R (PKR); oligoadenylate synthetase-2 (OAS2); RNAse-L, IFN-stimulated gene-15 (ISG15); IFN-induced proteins with tetratricopeptide repeats (IFIT1) and IFN-inducible transmembrane protein 3 (IFITM3), TLR3, RIG-I, MDA5, IRF3, IRF7, in nasopharyngeal swabs material and blood cells of patients on all tiers of treatment. Expression of ACE2 (receptor for SARS-Cov-2 entry) and potentially other genes involved in SARS-CoV-2 infection will be tested in nasopharyngeal samples.

# 2 BACKGROUND

## 2.1 Enhanced Risk of COVID-19 Mortality and Morbidity in Cancer Patients

Patients with cancer and COVID-19 had a 5-fold higher risk of severe events, defined as ICU admission requiring invasive ventilation or death, than those without cancer (1). Currently, there is no proven effective treatment of COVID-19 beyond supportive care. **This trial is based on the central premise that SARS-coronaviruses persist in host cells and in infected hosts by evasion of the innate antiviral responses mediated by RNAses (especially RNAse-L/OAS) and type-1 interferon (IFNα/β) pathway and IFN-stimulated genes (ISG), and that <u>early therapeutic activation of this pathway will limit viral replication and expansion in patients' tissues</u>, thus preventing severe complications.** SARS-Cov-2 is related to SARS, MERS, and other coronaviruses, which are positive-sense RNA viruses that generate dsRNA during replication. One of the principal IFN antiviral pathways involves activation of the host RNAses, especially RNase L, which is induced directly by dsRNA (predominantly by RIG-I and MDA5 helicases (2)) and indirectly by IFNα/β, degradation of viral RNA (3) and amplified IFNα/β production (2). Coronaviruses avoid upstream pathways that activate type 1 IFNs by cytosolic pattern recognition receptors (e.g. RIG-I and MDA5) preferentially activated by the coronavirus RNA (2, 4), and inhibition or avoidance of IRF3, a transcriptional factor that mediates the induction of type 1 IFNs, by that pathway (5-9). This inhibition of innate immune responses allows the virus to replicate in

host cells, and particularly in high risk patients, progress to pneumonia and respiratory failure. To overcome this barrier to effective immunity, we will evaluate combination rIFNα and rintatolimod. Rintatolimod, a selective dsRNA ligand of TLR3 (but not RIG-I/MDA5 (10)), has strong antiviral activity against multiple viruses, and was found to be protective in a lethal mouse model of SARS-CoV *in vivo*, and show strong anti SARS-CoV activity *in vitro* (11, 12). Combination rIFNα (INTRON® A; 20 MU/M$^2$ per infusion) and rintatolimod (200 mg per infusion), which showed synergy in activating IFN response signature in preclinical models (10) is being evaluated in clinical trials developed by Dr. Kalinski and colleagues for **patients with multiple solid tumors (active Roswell-held IND-112532 and trials NCT01545141, NCT03403634; NCT03403634), and, in over 70 enrolled patients, has not reached an MTD**.

The rationale for the combination therapy in cancer is based on strong synergy in inducing ISGs and other IFN-regulated genes and promoting type-1 immunity (10); activation of these same pathways is expected to augment antiviral defense in patients with COVID-19. While rintatolimod activates the TLR3/IRF3 pathway to induce IFNα, it does not activate the MAVS/RIGI/MDA5, the alternative RNA-virus-sensing pathway preferentially activated by the coronavirus RNA (2, 4), thus avoiding NF-kB and downstream cytokines (10) that could worsen acute lung injury in COVID-19. We expect INTRON® A to directly enhance the expression of OAS and its ability to promote the RNase L-mediated degradation of viral RNA in virally infected cells that do not mobilize own IFNα/β in response to COVID-19, while rintatolimod will induce TLR3-dependent ISGs in the uninfected bystander cells (10), and potentially infected cells, jointly leading to viral degradation. Augmentation of innate immunity in patients with COVID-19 is expected to avert viral progression to respiratory failure and mortality.

These results point to patients with cancer being at a several-fold higher risk for COVID-19-driven morbidity and mortality. Though many treatment modalities are being used, including single agent and combination antiviral agents and immunotherapy, there is no treatment proven to be effective for COVID-19 above supportive care. One promising option was use of HIV protease inhibitors for COVID-19; however, a recent trial showed lack of efficacy (13). Given the lack of effective therapies, there is an urgent need for more effective regimens that could be used prophylactically to prevent COVID-19 (e.g., vaccination) or as upfront therapy; this need is particularly pressing in patients with cancer. In addition, because there is no regimen shown to be more effective than supportive care, we did not include a comparator regimen.

### 2.2 COVID-19: Basic Biology and Rationale for Its Treatment Using the Rintatolimod (Ampligen®) and IFNα Combination

The COVID-19 is a coronavirus related to SARS, MERS, and other coronaviruses, which use RNA as their genetic material. It spreads in the body and in population by limiting early production of IFN and IFN-related genes, thus avoiding induction of host intracellular RNAse L (RNA-degrading enzyme that degrades cytoplasmic host and viral RNA) and activation of innate immunity. There is a large body of literature showing that coronaviruses inhibit upstream pathways that activate type 1 interferons, including inhibition of intracellular signaling driven by pattern recognition receptors (e.g. RIG-I and MDA5) that sense viral RNA and by inhibition of IRF-3, a transcriptional factor that induces the expression of type 1 interferons (5-9). This inhibition of innate immune responses is expected to allow the virus to replicate in epithelial cells, and particularly in high risk patients, progress to pneumonia and respiratory failure. Our goal is to use INTRON® A to directly activate RNAse L in virally infected cells with defective ability to

generate endogenous interferon-alpha, while rintatolimod, through ligation of TLR3, will stimulate interferon-alpha expression in bystander uninfected cells, thereby protecting them from viral infection. We also expect the synergy between these two factors in activating IFN-inducible genes, similar to our observations in cancer (10), amplifying the impact of IFNα in infected cells. Seen in this light, augmentation of innate immunity during early mild or moderately severe infection might avert progression to respiratory failure and mortality. In patients with more severe COVID-19, including those with respiratory failure, rintatolimod may promote viral clearance and avert worsening of lung injury. However, augmentation of innate immune responses may also worsen inflammatory lung injury in patients with COVID-19 infection, and therefore safety and efficacy are primary endpoints of this trial. **The current proposal involves repurposing of an investigational immunotherapy regimen developed by Dr. Kalinski for cancer (and currently being evaluated in several clinical trials) to be tested in patients with cancer and COVID-19 disease or significant exposure.**

**Interferon-alpha (INTRON® A)** and **rintatolimod [Ampligen®]** are two anti-viral drugs and immune activators, currently tested in combination in our ongoing the IRB- and FDA approved clinical trial I 52917 for patients with metastatic colorectal cancer and several other IRB- and FDA-approved trials in other cancers, performed at Roswell and the University of Pittsburgh.

Rintatolimod (selective TLR3 ligand, which activates multiple forms of antiviral immunity) has demonstrated strong antiviral activity against multiple viruses (*see the attached information from AIM*) including the coronavirus SARS COV-1 in vitro and in NIH-contracted animal experiments, conferring 100% protective survival. In vitro activity of Ampligen® against the human coronavirus, OC43, was performed by Barnard, D.L., et al. Proceedings of the 16th International Conference on Antiviral Research, 2003, using BS-C-1 kidney cells (African green monkey). In this in vitro test Ampligen® showed an **EC50 of 0.4 µg/ml compared to the easily achievable concentration in humans of 40 µg/ml, which is well tolerated**. In in vivo studies (11) and studies at NIH of SARS-COV-1 infected mice (12), Ampligen® conferred conferring a significant antiviral/survival effect.

Since COVID-19 shares key genomic and pathogenic similarities with SARS-COV-1 viruses (*see the attached information from AIM*), it is also expected to be susceptible to rintatolimod.

The second drug, **IFNα has shown antiviral activity** against multiple types of viruses, including other coronaviruses, and is **currently being tested as an anti-COVID-19 agent in multiple countries.**

The **rationale for the combination of these two drugs** in our ongoing clinical trials in cancer and in our proposed trial for COVID-19 patients results from **their strong synergy in inducing IFN-regulated genes and promoting type-1 immunity** (similarly needed for anti-viral and anti-cancer immunity) in human tissues *ex vivo* (10) and the activity of this combination observed in experimental animals (14), as well as the very good safety record of this combination observed in cancer patients so far (*see below*).

### 2.3 Past experience with IFNα and Rintatolimod

***Interferon–alpha*** (INTRON® A) is currently FDA approved for the adjuvant treatment of stage III melanoma. It has been examined by multiple investigators as an immune modulator in the setting of vaccine therapy with demonstrated safety (15). It has been extensively evaluated in the setting of metastatic CRC (as single agent or in combination with chemotherapy or IL-2), but was

shown to be largely ineffective (16-33) at daily doses ranging from 3-20 million units/$m^2$, administered subcutaneously or intravenously. In the treatment of melanoma, a small study by Astsaturov and colleagues (34) administered IFNα–2b in previously vaccinated melanoma patients, and was shown to convert immunization into objective clinical responses, suggesting its ability to amplify the effectiveness of local T cells infiltration and/or function at the tumor site. Vaishampayan et al. examined IFNα-2b 5 million units subcutaneously three times a week following vaccination with a melanoma vaccine (Melacine) (35). Treatment at this dose was well tolerated. Similarly Mitchell et al. recently completed a large trial examining IFNα-2b, 5 million units subcutaneously three times a week for one year (36). Di Pucchi and Pilla similarly examined the combination of a melanoma peptide vaccine with IFNα-2b, 3 million units subcutaneously three times a week, with little to no toxicity.

We propose to include a short course of high dose interferon alpha-2b (with the dose-escalation lead-in [0-5-10-20] and with maximum 20 million units/$m^2$, IV, on Days 1 and 3). The maximum dose of 20 million units/$m^2$ is similar or lower than the previously evaluated doses in melanoma patients (37-39). In this group of patients, in accordance with previous reports, we expect to consistently observe flu-like symptoms. However, this regimen hasn't been evaluated in patients with respiratory viral infection, and additional AEs may be observed. Specifically, augmentation of innate immune responses may also worsen inflammatory lung injury in patients with COVID-19 infection, and therefore safety and efficacy are primary endpoints of this trial.

***Rintatolimod*** (Selective toll-like receptor-3 [TLR3] Ligand; analog of poly IC with reduced toxicity for i. v. use).

Rintatolimod (Ampligen®) is a TLR3 specific Poly IC analog in which the cytidylic acid chain has uridylic acid substitutions at a molar ratio of 12:1. Chemokine modulation in temporal association with type I interferon administration is observed with this agent. Rintatolimod has been studied extensively in multiple clinical settings including cancer, chronic viral infection, vaccination protocols, and in chronic treatment of chronic fatigue syndrome.

Rintatolimod has been generally well tolerated with only a low incidence of clinical toxicity. Clinical experience with rintatolimod now totals over 800 patients with more than 200 patients receiving rintatolimod for up to one (1) year, over 50 patients up to two (2) years, and more than 20 patients over two (2) years.

The proposed dosage of 200 mg IV is the starting dose used in chronic treatment of Chronic Fatigue Syndrome (CFS). That dose is escalated to 400 mg IV twice weekly for the CFS indication; however, for use as a chemokine modulator, pharmacologic peak serum levels are achieved at 200 mg; thus, 200 mg daily for 3 days will be incorporated for the immune modulation regimen. Preclinical evidence demonstrates the synergy between IFNα and rintatolimod in inducing the production of the effector T cell-attracting chemokines.

### 2.4 Clinical experience with Rintatolimod (Ampligen®) in Combination with Interferon Alpha-2b and Celecoxib

NCT01545141 (UPCI 10-131) was a Phase I study which evaluated the combination of rintatolimod, interferon-alpha 2b, and celecoxib administered for one course over 5 days, prior to tumor resection. The **Phase I study was completed, with escalation to the maximal planned dose, without the emergence of undue toxicity**. A 5-day regimen consisting of rintatolimod 200

mg IV daily, interferon alpha-2b (20 million units/ $m^2$) IV daily and celecoxib 200 mg po bid was deemed **highly tolerable and suitable for further investigation**.

In addition to the demonstrated safety, preliminary evidence of biologic efficacy was observed. Individuals who were treated with CKM prior to resection, demonstrated an improvement in intratumoral CD8/FOXP3 ratios as well as CXCL10/CCL22 ratios when compared to nonrandomized controls, treated with standard care at the University of Pittsburgh (*Zureikat, Bartlett and Kalinski, manuscript in preparation*). The design (neo-adjuvant treatment) and numbers of patients treated do not permit any meaningful estimate of clinical outcomes or radiographic response at this time.

In addition to the evaluation of rintatolimod, interferon alpha-2b administered i. v. (combined with oral Celecoxib) for one course over 5 days, as a stand-alone treatment, the same combinations (but different administration regimens) are being evaluated as a part of combinatorial regimen (with DC vaccines) in additional patients with peritoneal carcinomatosis (NCT02151448 / UPCI 12-110). Clinical trial NCT02151448 (over 50 patients evaluated so far) involve multiple cycles of DC vaccines followed by 4-day long cycles of IFN-a/celecoxib regimen, with rintatolimod administered on Days 2 and 4 of each cycle).

No DLTs have been observed in either of these trials, and we consider the INTRON® A dose of 20MU/M2 as recommended i.v. dose for combination with i.v. rintatolimod. **These concentrations of INTRON® A (20MU/M2) plus rintatolimod (200 mg) are being used in combination in our ongoing trials at Roswell Park** in colon and breast cancer and in a recently approved trial in prostate cancer:

- **I 52917 (**NCT03403634; IND 112532) Phase 2A Study Evaluating a Chemokine-Modulatory Regimen in Patients with Colorectal Cancer Metastatic to the Liver. (Sarbajit Mukherjee and P. Kalinski)

  Status: COMPLETED; MANUSCRIPT IN PREPARATION

  Phase: Phase IIa (combination with Celecoxib).

- **I 62218 (NCT03403634)** Chemokine Modulation Therapy and Pembrolizumab in Treating Participants with Metastatic Triple-Negative Breast Cancer. (Shipra Gandhi and P. Kalinski)

  Status: CLOSED TO ACCRUAL

  Phase: Phase IIa (combination with Celecoxib and Pembrolizumab).

- **I 73718** Phase I Clinical Trial Assessing the Combination of Chemokine Modulation with Neoadjuvant Chemotherapy in Triple Negative Breast Cancer **IND 145344).** (Shipra Gandhi and P. Kalinski)

  Status: COMPLETED; MANUSCRIPT IN PREPARATION

  Phase: Phase I (combination with Celecoxib and Paclitaxel).

- **I 77318 (NCT03899987)** Aspirin and rintatolimod With or Without Interferon-alpha 2b in Treating Patients with Prostate Cancer Before Surgery" (Gurkamal Chatta and Pawel Kalinski)

  Status: FDA (IND 143104) and IRB approved. ACCRUING PATIENTS

### 2.5 Rationale for eliminating celecoxib from the proposed regimen and for reducing, eliminating, or changing the source and route of administration of IFNα

In view of the potential concerns regarding the use of NSAIDs in patients with COVID-19, we decided not to include Celecoxib in the current trial.

The dose of INTRON® A IFNα may be reduced from 20MU/$m^2$ to 5 MU/$m^2$ or to 0), in case of any observed toxicities, or in case of IFNα shortage.

In case of potential shortages, INTRON® A may be replaced by another form of IFNα at the same (Units) dose. In case the only available IFNα is formulated for an alternative route of administration (e.g., subcutaneous), we will adjust the dose to use the most common dose for that specific product. An IRB amendment will be submitted for any changes in formulation or dosing.

### 2.6 Overall Impact

Our study focuses on patients with cancer, but knowledge gained about safety and immunologic correlates is expected to be applicable to other patients at high risk for COVID-19-related morbidity and mortality as well as to future viral pandemics. Using each patient's baseline nasopharyngeal viral load, we will evaluate to what extent the study regimen reduces viral load relative to supportive care only. Assessment of nasopharyngeal viral load at multiple time points will enable evaluation of early and long-term effects of the study regimen in controlling viral replication. A reduction in nasopharyngeal viral load by PCR may also reflect reduced likelihood of transmission of virus to others. As described in the Statistical Plan (Section 19), the study is non-randomized and each patient will serve as their own control regarding baseline, on-treatment, and post-treatment nasopharyngeal viral load. In addition, comparisons will be made with historical controls in which Roswell Park patients with COVID-19 were treated with standard of care and longitudinal viral load was monitored as standard of care. As described in the demonstration of safety of this regimen and reduction of nasopharyngeal viral load will establish the foundation for a larger randomized trial powered for clinical efficacy, such as reduction in respiratory failure and mortality.

Our study will enroll patients with cancer with varying comorbidities and levels of COVID-19 severity. For outpatients with COVID-19 at high risk for severe complications based on age and co-morbidities, a monoclonal antibody cocktail (e.g. Regeneron's combination of casirivimab and imdevimab) is standard of care. In patients with more severe COVID-19 who are hospitalized and require supplemental oxygen, therapy is focused on controlling inflammatory injury. Dexamethasone was associated with a survival benefit and will be administered to all patients who meet criteria for this agent. Other anti-inflammatory agents such as IL-6-targeting agents and baricitinib can also be of value, although their benefit when added to corticosteroids is unclear. The antiviral agent, remdesivir, is of unclear value based on conflicting data; at best it shortens the duration of illness but doesn't have a survival benefit. At Roswell, we routinely administer combination dexamethasone and remdesivir to inpatients with significant COVID-19, and will do so for patients enrolled in this protocol unless there is a clinical contraindication to receiving either agent. The data on convalescent plasma is also contradictory, but plasma with high neutralizing titers against the viral Spike protein is likely to be of value. We do not know the effect of these standard of care regimens on nasopharyngeal viral load in patients with cancer. In addition, since these regimens are often administered concurrently, it's difficult to delineate the effect of a specific drug on viral load. Based on our experience at Roswell Park, the nasopharyngeal viral load in some

immunocompromised patients with cancer (e.g. stem cell transplant recipients and patients receiving B-cell-depleting agents), has persisted for several weeks despite receiving combinations of these agents (e.g. remdesivir and dexamethasone, often in combination with convalescent plasma). The standard of care for COVID-19 changes over time. Regarding the current protocol, the study regimen will be added to what in our judgment is the best standard of care regardless of outpatient or inpatient status.

# 3 INCLUSION AND EXCLUSION CRITERIA

## 3.1 Inclusion Criteria (Main Cohort)

To be included in this study, participants must meet the following criteria:

1 Patients with cancer, with the exception of patients with active acute leukemia and allogeneic hematopoietic stem cell transplant recipients. Patients may be on active therapy or received therapy (e.g., chemotherapy, radiation, or surgery) within 7 years. Patients with active cancer who have not yet been treated (e.g. newly diagnosed cancer or early stage MDS or CLL) are eligible. Basal cell cancer and carcinoma in situ treated with local excision alone do not qualify for inclusion.

2 Presence of symptomatic infection, defined by fever (T≥38.0°C ) OR respiratory symptoms (cough, nasal congestion, or shortness of breath), OR lung infiltrates on chest X-ray or CT imaging, Diagnosis of COVID-19 is based on PCR testing of respiratory samples.

3 Age equal to ≥ 18 years or older (children are excluded because COVID-19 typically has a milder course in children, and lack of safety data of this regimen in children).

4 Laboratory evaluation:

- Platelet ≥ 75,000/μL
- Hemoglobin ≥ 9 g/dL
- Hematocrit ≥ 27%
- Absolute Neutrophil Count (ANC) ≥ 1000/μL
- Creatinine clearance ≥ 50 mL/min (Cockroft-Gault Equation–note: plasma creatine instead of serum is used at Roswell Park)
- Total bilirubin ≤ 2 X institutional ULN
- AST (plasma) and ALT(plasma) ≤ 2 X institutional ULN
- Plasma amylase and lipase ≤2 X institutional ULN

5 In the absence of COVID-19, a life expectancy of 6 months is expected.

6 Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

**NOTE:** For blood chemistry labs, Roswell Park clinical blood chemistries are performed on plasma unless otherwise indicated.

Refer to **Appendix D** for the Investigator Study Eligibility Verification Form (Main Cohort): Inclusion Criteria.

### 3.2 Exclusion Criteria (Main Cohort)

Participants will be excluded from the study for the following:

1 Patients with severe COVID-19 infection defined by pulmonary infiltrates on Chest X-Ray or CT imaging plus one of the following: room air $SaO_2 \leq 92\%$, room air $PaO_2 < 70$ mm Hg, or $PaO_2$-$PaO_2 \geq 35$ mm Hg.

2 Contraindication to r-IFNα based on prior hypersensitivity, autoimmune hepatitis, decompensated liver disease.

3 Patients who have active acute myeloid leukemia or acute lymphoid leukemia or are allogeneic hematopoietic stem transplant recipients. Acute leukemia in remission and chronic leukemias are not exclusion criteria.

4 Cardiac events:

   a. Acute coronary syndrome, myocardial infarction, or ischemia within past 3 months,

   b. New York Heart Association classification of III or IV congestive heart failure (**Appendix A**)

5 Unwilling or unable to follow protocol requirements.

6 Patients with known serious mood disorders.

7 Any additional condition, such as pre-existing inflammatory lung disease, which in the Investigator's opinion deems the participant an unsuitable candidate to receive the study drugs.

8 Concurrent infections, e.g. bacterial pneumonia or sepsis, that would make it difficult to evaluate clinical response to therapy or study drug toxicities.

9 Therapies known to cause cytokine release syndrome (CRS), e.g. engineered T cells, within 30 days.

10 Patients at high risk for tumor lysis syndrome.

11 Concurrent active pneumonitis predating COVID-19, such as from checkpoint inhibitor therapy, chemotherapy-associated toxicity, or radiation pneumonitis.

12 Autoimmune disease that requires systemic immunosuppression.

13 Protocol-defined baseline abnormalities in cell counts, renal, or hepatic function.

14 Any additional condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive the study drugs.

Refer to **Appendix E** for the Investigator Study Eligibility Verification Form (Main Cohort): Exclusion Criteria.

### 3.3 Inclusion Criteria (Expansion Cohort: Rintatolimod Plus Best Available Standard Care)

We have added an expansion cohort to receive rintatolimod plus best available standard care. Because rIFN-α is not included in this group, eligibility criteria have been liberalized to include patients with more severe COVID-19, including those with respiratory failure, and exclusion criteria specific to rIFN-α have been removed. For patients who are eligible for both the main cohort and expansion cohort, enrollment in the Main Cohort will be prioritized because of the rationale that it might be more effective. To be included in the Expansion Cohort, cancer participants must meet the following criteria:

1 Patients with cancer or allogeneic stem cell transplant recipients with and without a cancer diagnosis.

- Patients with cancer may be on active therapy or received therapy (e.g., chemotherapy, radiation, or surgery) within 7 years.
- Patients with active cancer who have not yet been treated (e.g. newly diagnosed cancer or early stage MDS or CLL) are eligible.
- Basal cell cancer and carcinoma in situ treated with local excision alone do not qualify for inclusion.

2 Presence of symptomatic infection, defined by fever (T≥38.0°C ) OR respiratory symptoms (cough, nasal congestion, or shortness of breath) OR lung infiltrates by chest X-ray or CT imaging. Diagnosis of COVID-19 is based on PCR testing of respiratory samples. Severe infection is excluded (see Exclusion Criteria).

3 Age equal to ≥ 18 years or older (children are excluded because COVID-19 typically has a milder course in children, and lack of safety data of this regimen in children). In the absence of COVID-19, a life expectancy of 6 months is expected.

4 Participant or health care proxy must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure. There may be specific instances when the patient can't provide informed consent, e.g. they require mechanical ventilation and are sedated, in which case a health care proxy will be able to provide informed consent. Patients with temporary cognitive impairment will be consented once their capacity has returned**.** Patients with chronic cognitive impairment, e.g. dementia, that precludes informed consent will not be enrolled.

**NOTE:** For blood chemistry labs, Roswell Park clinical blood chemistries are performed on plasma unless otherwise indicated.

Refer to **Appendix D** for the Investigator Study Eligibility Verification Form (Expansion Cohort): Inclusion Criteria.

### 3.4 Exclusion Criteria (Expansion Cohort)

Participants will be excluded from the study for the following:

1 Patients with respiratory failure requiring mechanical ventilation with FIO2 of > 60%.

2 Allogeneic hematopoietic stem cell transplant recipients with active pulmonary GvHD (any grade).

3 Cardiac events:

a. Acute coronary syndrome, myocardial infarction, or ischemia within past 3 months,

b. New York Heart Association classification of III or IV congestive heart failure (**Appendix A**)

4 Unwilling or unable to follow protocol requirements.

5 Any additional condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive the study drugs.

Refer to **Appendix E** for the Investigator Study Eligibility Verification Form (Expansion Cohort): Exclusion Criteria.

### 3.5 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this study.

### 3.6 Special Populations

The following special populations will be excluded:

- Chronically cognitively impaired adults (e.g. those with dementia) with impaired decision-making capacity
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

## 4 LOCAL AND STUDY-WIDE NUMBER OF SUBJECTS

Maximum number of Roswell Park subjects: The anticipated number of subjects required for the main portion of the study is 44. All patients must have cancer and need not be established Roswell Park patients. The modification of the protocol triggered by the observed high effectiveness of the treatment in the first patient who received rintatolimod alone will include additional 20 cancer patients (Expansion Cohort).

### 4.1 Target Accrual

**Main Cohort:** Up to 44 patients are expected to be needed to estimate the biologic impact of this regimen and establish a preliminary estimate of efficacy. This number includes the following tiers of the dose-escalation of IFNα (3+3 design with 0, 5 MU/M$^2$, 10 MU/M$^2$, and 20 MU/M$^2$). Once an MTD is established, subsequent patients (n = 10) will receive rintatolimod + IFNα (at the MTD or, in the absence of an MTD, at 20 MU/M$^2$ IFNα) as well as standard of care. Total accrual time is expected to take 36 months.

**Expansion Cohort:** In addition, we will accrue a maximum of 20 patients on Expansion Cohort, who will receive rintatolimod and best available standard care.

# 5 LOCAL AND STUDY-WIDE RECRUITMENT METHODS

## 5.1 Recruitment

Subjects will be recruited from Roswell Park and our affiliate practices, and University at Buffalo-affiliated hospital systems. Recruitment efforts will focus on patients with initial signs of COVID-19 who would be offered enrollment as soon as feasible. In addition, asymptomatic patients with contact (e.g., household member or health care-associated exposure) with COVID-19 will be monitored for development of symptoms or signs of COVID-19 that would result in nasopharyngeal swab PCR testing: Roswell Park is a New York State-designated regional laboratory for COVID-19 PCR-based testing with same or next day reporting of results.

Men and women will be recruited, with age, race, and socioeconomic status expected to reflect the general Roswell Park patient population.

# 6 MULTI-SITE RESEARCH

The study will be opened at Roswell Park first to obtain preliminary safety data and establish feasibility, but we may prospectively partner with other cancer centers as study sites in regions with established community-based transmission of COVID-19.

# 7 STUDY TIMELINES

Main Cohort: A maximum of 44 evaluable participants will be enrolled to the study over up to 36-months. Patients will be followed until Day 30 after initiation of the study regimen.

Expansion Cohort: A maximum of 20 evaluable participants will be enrolled to the study over up to 36-months. Patients will be followed until Day 30 after initiation of the study regimen.

Enrollment in the Main Cohort and Expansion Cohort will be done concurrently. If a patient is eligible for enrollment in both the Main and Expansion Cohort and is willing to be enrolled in either cohort, priority will be given to the Main Cohort.

# 8 STUDY ENDPOINTS

## 8.1 Primary Endpoints

- The primary safety endpoints are frequency of grade 3 or 4 AEs considered to be probably or definitely related to the treatment regimen.
- Evaluate kinetics of viral load expressed as Ct values in nasopharyngeal swab samples in the course of treatment and Days 7 and 14. (40)

## 8.2 Secondary Endpoints*

- Clinical efficacy will be assessed by the frequency of these complications: (i) progression of infection requiring hospitalization; (ii) respiratory failure requiring mechanical ventilation; and (iii) death within 30 days.

Although the data on outcomes in patients with COVID-19 and cancer are limited, based on the Chinese experience, approximately 40% are expected to have the composite endpoint of respiratory failure requiring mechanical ventilation or death (1). We note the limitations of this

estimate regarding small numbers of patients with cancer and heterogeneity in cancer types and co-morbidities, including older age, smoking, and lung disease (41). If present, acute respiratory distress syndrome (ARDS) will be graded by Berlin criteria (42), which include 3 mutually exclusive categories of ARDS based on degree of hypoxemia: mild (200 mm Hg < $PaO_2/FIO_2 \leq$ 300 mm Hg), moderate (100 mm Hg < $PaO_2/FIO_2 \leq$ 200 mm Hg), and severe ($PaO_2/FIO_2 \leq$ 100 mm Hg). The degree of ARDS is has been validated as a predictor of mortality in patients with respiratory failure. The Berlin criteria require 5cm $H_2O$ as the minimum level of PEEP delivered by a ventilator or CPAP for diagnosing ARDS; if PEEP is not administered, then ARDS cannot be diagnosed. In addition, the Berlin criteria require excluding hydrostatic pulmonary edema by clinical judgement or with echocardiograph as a cause of respiratory failure. Although the study is not powered for the clinical endpoint, in case that any of the elements of the clinical efficacy endpoint will reach statistical difference between arms, such clinical endpoint will be considered as an overruling endpoint of efficacy

- Evaluate kinetics of viral load as Ct values in peripheral blood in the course of treatment and Days 7 and 14 (40).
- Determine the kinetics of changes of the immune subsets and circulating inflammatory mediators (including CRP, cytokines, chemokines, interferons) in peripheral blood in the course of treatment. Plasma and PBMCs will be cryopreserved for future exploratory studies, including the assessment of intracellular signaling and TCR and BCR repertoires as correlates of response to the study regimen.
- Determine the induction of known mediators of antiviral immunity that include (myxovirus resistance gene, MxA; protein Kinase R (PKR); oligoadenylate synthetase-2 (OAS2); RNAse-L, IFN-stimulated gene-15 (ISG15); IFN-induced proteins with tetratricopeptide repeats (IFIT1) and IFN-inducible transmembrane protein 3 (IFITM3), TLR3, RIG-I, MDA5, IRF3, IRF7, in nasopharyngeal swab material and blood cells of patients on all tiers of treatment. Expression of ACE2 (receptor for SARS-Cov-2 entry) and potentially other genes involved in SARS-CoV-2 infection will be tested in nasopharyngeal samples.

## 9 STUDY DESIGN

The antiviral efficacy of the combination of interferon alpha-2b and rintatolimod will be evaluated by administering fixed doses of each drug. Subjects will receive 1 day of the combination (Day 1), followed by 1 day of observation and the same regimen on Day 3 (or Day 4). according to the safe established dosing levels (**see Table 1**). During this time, subjects will be monitored continuously for safety (refer to **Section 19.2.1**). As the standard of care therapy for COVID-19 is evolving, all patients will receive optimal standard of care that will be administered concurrently with the study drug regimen. In a double-blind, randomized, multi-center, placebo-controlled trial of intravenous remdesivir in adults hospitalized with COVID-19 with evidence of lower respiratory tract involvement, remdesivir treatment resulted in shortening the time to recovery by 4 days (43). Though 14-day survival was greater in remdesivir recipients, the difference was not statistically significant (43). Adults hospitalized with COVID-19 with evidence of lower respiratory tract involvement will be offered remdesivir through an EUA if and when this drug is available to us. If we're not able to offer remdesivir to all patients based on drug availability, we expect a similar proportion of patients in the study drug and control arms to have received remdesivir, and the effect of remdesivir on study endpoints will be evaluated in an exploratory fashion.

In a multi-center controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with COVID-19, patients were randomly assigned to receive oral or intravenous dexamethasone (6 mg daily) for up to 10 days or to receive usual care alone (44). Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization ($p < 0.001$). The survival benefit of dexamethasone was observed among patients receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. Based on these results, dexamethasone (6 mg/day) will be given as standard of care to patients admitted with COVID-19 who require supplemental oxygen.

Nasopharyngeal swab collection: Nasopharyngeal swabs will be performed by trained nursing staff under full PPE precautions. Nasopharyngeal swabs will be obtained using a single swab for both nostrils as specified in CDC guidelines: https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html. Swabs are placed in viral media and submitted immediately on room air to the Dept. of Laboratory Medicine at Roswell Park. RT-PCR for SARS-CoV-2 testing is done under the direction of Dr. Jan Nowak (Professor of Oncology, Pathology, and Molecular Pathology). Testing for SARS-CoV-2 at Roswell Park received New York State (NYS) EUA. Roswell Park uses the New York SARS-CoV-2 Real-time RT-PCR Diagnostic Panel, which received EUA from the FDA. As a NYS-authorized laboratory for COVID-19 testing, Roswell Park's diagnostic methods are as stipulated in the New York SARS-CoV-2 Real-time RT-PCR Diagnostic Panel authorized procedures. The N1 and N2 PCR reactions target different regions of the SARS CoV-2 RNA. The New York SARS-CoV-2 Real-time RT-PCR Diagnostic Panel requires the following control materials:

- Human Specimen Control (HSC): A human cell culture preparation used as an extraction control and positive control for the RNase P primer and probe set that is extracted and tested concurrently with each specimen extraction run.
- SARS-CoV-2 Positive Control (SARS-CoV-2 Pos): Run with each batch of specimens. Monitors improper assay setup, reagent failures of rRT-PCR reagents and reaction conditions.
- No Template Control (NTC): Nuclease-free water included in each run. Monitors for reagent and system contamination.
- RNase P (RP) control in clinical samples: The RP primer and probe set is included in each run to test for human RNase P, which controls for specimen quality and demonstrates that nucleic acid was generated by the extraction process.

Two PCR reactions using N1 and N2 primer sets target different regions of the SARS CoV-2 RNA. A specimen is considered positive if both N1 and N2 Ct values are < 40. Specimens with one value <40 and one >40 after repeat testing are interpreted as "Inconclusive". Specimens which are negative show no amplification for both N1 or N2 PCR reactions. Based on our experience, N1 Ct values are typically several cycles lower than the N2 values, and therefore N1 Ct values will be used in statistical analyses.

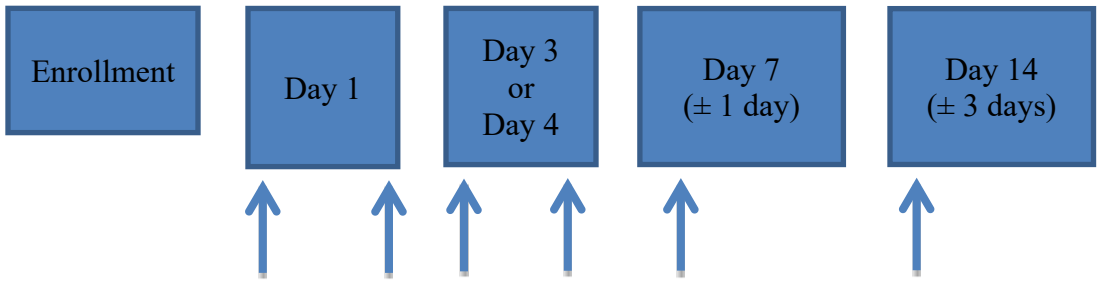
*Validation studies included in the assay IFU (Instructions For Use) (https://www.fda.gov/media/134922/download) establish a Limit of Detection (LoD) of 25 genome copies/reaction. In defining the performance characteristics of the test, the IFU shows that this limit typically correlates with Ct values below 40 cycles. To assure test performance

consistency, positive target controls and extraction controls are required to show Ct values < 40 cycles for test run validation. Specimens with one value <40 and one >40 after repeat testing are interpreted as "Inconclusive".

**Table 1 Dosing**

| | |
|---|---|
| For the Main Cohort: Interferon alpha-2b dose-escalation IV over 20 minutes on Day1 and on Day 3 or 4. The dose-escalation will use a standard 3 + 3 design, with the following doses: 0, 5, 10, and 20 MU/M$^2$.<br>Subsequent patients receive IFNα at 20 MU/M$^2$ or at MTD + rintatolimod (200 mg) on Day 1 and on Day 3 (or 4) as well as standard of care. | Initial administration to start at 20 mL/ hour and increase to 40 mL/ hour after 30 minutes as per the standard at Roswell. Total duration of rintatolimod infusion: 2.5 h-3h. Tubing should be flushed with 30 to 50 mL of normal saline solution upon completion. Administration will be followed by 1 hour of observation and vital signs at 30 and 60 minutes post-infusion (± 5 minutes). |

**Figure 1 Study Schema (Main Cohort)**




**Specimen collections (blood, nasopharyngeal swabs).**

Patients will be seen for an end of treatment visit on Days 7 and 14 to review adverse events and clinical outcome of therapy.

Following the implementation of this protocol, we observed:

1. Difficulty to accrue patients with cancer and original inclusion criteria, as a result of strict inclusion criteria reflecting contra-indications for IFNα use.
2. The first patient treated at a lowest tier cleared the virus already on Day 3 of treatment before the administration of the second dose of the vaccine.

In this situation, the current modification of the protocol includes an additional 20 cancer patients (Expansion Cohort), which will receive **of rintatolimod as well as Standard of Care**. The inclusion criteria are different than the main protocol.

# 10 TREATMENT

All patients will receive best available standard of care. Depending on the severity of COVID-19 and need for hospitalization, standard of care can include, but is not limited to, monoclonal antibody formulations directed against the SARS-CoV-2 Spike protein, remdesivir, dexamethasone, and tocilizumab. Treatment in the Main Cohort will consist of lead-in single agent rintatolimod (first 3 patients on the dose-escalation component) followed by the combination of rintatolimod and dose-escalation of rIFNα. Intravenous (IV) rintatolimod is administered as a fixed dose (200 mg per infusion) and IV rIFNα dose-escalation will be a standard 3 + 3 design, with the following doses per infusion: 0, 5, 10, and 20 MU/M$^2$. The dose-escalation phase will lead to which patients will receive IFNα at 20 MU/M$^2$ or at MTD + rintatolimod (200 mg). The regimen will be administered on Day 1 and on Day 3 (or 4), and EOT assessments will occur on Day 7 (± 1 day) and Day 14 (± 3 days). This portion of the study will allow for additional safety data and the analysis of the effect of the study regimen on nasopharyngeal viral load. Using each patient's baseline nasopharyngeal viral load, we will evaluate to what extent the study regimen reduces viral load relative to supportive care only.

Treatment in the Expansion Cohort will be IV rintatolimod is administered as a fixed dose (200 mg per infusion on Day 1 and on Day 3 (or 4). Based on the PI's judgment, additional infusions of rintatolimod at 200 mg may be administered 3 to 4 days apart. Decisions about additional rintatolimod infusions will be based on evaluation of AEs attributed to rintatolimod, particularly increased FIO2 needs. A maximum of 12 rintatolimod infusions may be administered per patient. The rationale for a maximum of 12 infusions was based on discussions with leadership from AIM Immunotech regarding the expected effects of rintatolimod on innate immune responses over time based on data from patients with and without cancer. Rintatolimod activates innate immune responses through a number of mechanisms including activation of RNase L and inducing interferon stimulated genes (ISGs). Administration of rintatolimod over a number of weeks may be required for sustained activation of innate immune responses to clear SARS-CoV-2.

## 10.1 Dosing and Administration

### Interferon-Enhancing Regimen

For dosing, refer to **Table 1**. The regimen will be administered on Days 1 and 3 (or 4) in the following order:

- Pretreatment: 500 mL Normal saline IV over 60 minutes
- Pre-medications: acetaminophen (Tylenol®) 650 mg by mouth x 1 dose; prochlorperazine (Compazine®) 10 mg by mouth x 1 dose – administered 30 minutes (±5 minutes) after starting pre-treatment hydration
- Interferon alpha-2b: (dose-escalation; maximum 20 MU/M$^2$) IV over 20 minutes

Rintatolimod: 200 mg IV, initial administration to start at 20 mL/ hour and increase to 40 mL/ hour after 30 minutes as per the standard at Roswell. Total duration of rintatolimod infusion: 2.5 h-3h. Tubing should be flushed with 30 to 50 mL of normal saline solution upon completion. Administration will be followed by 1 hour of observation and vital signs at 30 and 60 minutes post-infusion (± 5 minutes).

Pretreatment and pre-meds listed above are recommendations and may be modified based upon institutional SOC requirements and at the discretion of the investigator. Treatment can be administered in the outpatient or inpatient setting, per the investigator's/physician's discretion.

Each daily treatment will be initiated after interval history and physical examination is performed and once the relevant laboratory studies have been confirmed to be within clinically acceptable ranges, specifically: ANC $\geq 1000/mm^3$, total bilirubin $\leq$ 3x ULN, AST and ALT $\leq$ 5 x ULN.

**Expansion Cohort (Rintatolimod plus best available standard of care)**

20 patients on Expansion Cohort will receive rintatolimod plus best available care.

Pretreatment for rintatolimod will be:

- 500 mL Normal saline IV over 60 minutes
- Pre-medications: acetaminophen (Tylenol®) 650 mg by mouth x 1 dose; prochlorperazine (Compazine®) 10 mg by mouth x 1 dose – administered 30 minutes (±5 minutes) after starting pre-treatment hydration

Rintatolimod: 200 mg IV, initial administration to start at 20 mL/ hour and increase to 40 mL/ hour after 30 minutes as per the standard at Roswell. Total duration of rintatolimod infusion: 2.5 h-3h. Tubing should be flushed with 30 to 50 mL of normal saline solution upon completion. Administration will be followed by 1 hour of observation and vital signs at 30 and 60 minutes post-infusion (± 5 minutes).

Pretreatment and pre-meds listed above are recommendations and may be modified based upon institutional SOC requirements and at the discretion of the investigator. Treatment can be administered in the outpatient or inpatient setting, per the investigator's/physician's discretion.

### 10.2 Dose Modification

Based on our experience with the combination of rintatolimod and INTRON® A as anti-cancer treatment (over longer periods of time than the currently proposed trial for COVID-19), we do not expect the need for dose modifications. However, in case of specific toxicities, dose modification rules will be used (**Table 2**). Taking into account that the rationale for the regimen is a short-term intervention to augment antiviral immunity for an acute viral infection, we do not plan for re-escalations or administration of any missing doses after successful management of toxicities. Since the progression of COVID-19 is believed to be facilitated by lack of the activation of innate immunity (IFN responses and RNases), we anticipate that even transient (or lower intensity) activation of these pathways may help to better control the viral spread. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0).

Therapy will be immediately discontinued for any grade IV treatment-related toxicity that becomes apparent. In the event of any adverse effect, appropriate medical treatment will be instituted and study treatment will be discontinued based on physician judgment.

**Table 2 Treatment Related Toxicity Management**

| Treatment-related AEs | Toxicity grade or conditions (CTCAE5.0) | Action taken for Interferon Alpha-2b | Action taken for Rintatolimod | Additional actions |
|---|---|---|---|---|
| Chills/Fever | Grade 3 that persists for ≥ 48 hours despite acetaminophen | None | None | Consider additional acetaminophen dosing, supportive care |
| Pancreatitis | Grade 3 | Hold<br><br>Decreased future doses by 75% (to 5MU/M2) | Hold | Supportive measures as clinically indicated |
| AST / ALT elevation or Increased bilirubin | Grade 3 | Hold until improved to grade 1; Decrease future doses by 75% | Hold | Advise evaluation for other possible etiologies; consider imaging |
| Vomiting | Grade 3 vomiting ≥ 48 hours despite optimal anti-emetic therapy | Hold until resolved to grade 1; Decrease future doses by 75% | Hold | |
| Depression or other clinically relevant mood disorder | Grade 3 | Permanently discontinue; appropriate supportive care/intervention | None | Patients and family members will be informed in advance about the potential for depression and anxiety, including worsening of pre-existing mood disorders. |
| Neutropenia | Grade 3 or 4 | If Grade 3, decrease future doses by 75%. If Grade 4, permanently discontinue | Hold | Transient neutropenia is expected as a result of neutrophil activation and redistribution rather than bone marrow suppression. Recent cytotoxic chemotherapy is an additional cause of neutropenia. COVID-19 is known to cause lymphopenia, but not neutropenia. For prolonged neutropenia that is not expected from the study regimen and recent chemotherapy (if applicable), the primary oncologist and a hematologist will be consulted. |
| Hemorrhage | Grade 2 or greater | None | None | |
| Myocardial infarction, stroke, | | Permanently discontinue; appropriate | Permanently discontinue; appropriate | |

| Treatment-related AEs | Toxicity grade or conditions (CTCAE5.0) | Action taken for Interferon Alpha-2b | Action taken for Rintatolimod | Additional actions |
|---|---|---|---|---|
| or other arterial thrombotic event | | supportive care/intervention | supportive care/ intervention | |
| All other clinically significant AEs[1] | Intolerable Grade 2 or Grade 3 | Hold therapy until resolved to Grade 1 or baseline; reduce future doses by 75% | Hold therapy until resolved to Grade 1 or baseline; reduce future doses by 50% | |
| | Grade 4 | Permanently Discontinue | Permanently Discontinue | |
| **Cytokine Release Syndrome[2]** | ≥ Grade 2, based on the Penn scale (45) | Permanently Discontinue | Permanently Discontinue | In discussion with the primary oncologist, tocilizumab, corticosteroids, and potentially other immunomodulators will be used based on clinical judgement for ARDS and CRS-like complications. |

[1] Transient neutropenia is known to occur with rIFN-α and may reflect increased neutrophil migration to sites of infection or the tumor microenvironment as well as the effect of IFN-α on neutrophil survival and lifespan (46). This transient neutropenia has not been associated with an increased risk of infection.

2 Refer to: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5833070/ (Porter D, Frey N, Wood PA, Weng Y, Grupp SA. Grading of cytokine release syndrome associated with the CAR T cell therapy tisagenlecleucel [published correction appears in J Hematol Oncol. 2018 Jun 13;11(1):81]. J Hematol Oncol. 2018;11(1):35. Published 2018 Mar 2. doi:10.1186/s13045-018-0571-y).

### 10.2.1 Interferon Alpha-2b and/or rintatolimod Non-hematologic toxicities

Considered to be possibly, probably, or definitely related to interferon alpha-2b and rintatolimod:

- **Interferon Alpha-2b:**

  For grade 3 toxicity not addressed in **Table 2**:

  - 1st episode: dose will be held and restarted at the next study visit at a dose reduction by 75%. The dose can be re-escalated if toxicity is reduced to ≤ grade 1 or baseline.
  - 2nd episode: Treatment will be discontinued.

  For grade 4 toxicity

  - Treatment will be discontinued

- **Rintatolimod:**

  For grade 3 toxicity not addressed in **Table 2**:

  - 1st episode: dose will be held and restarted at the next study visit at a dose reduction by 50%. The dose can be re-escalated if toxicity is reduced to ≤ grade 1 or baseline.
  - 2nd episode: Treatment will be discontinued.

  For grade 4 toxicity:

  - Treatment will be discontinued

### 10.2.2 Definition of DLT

Treatment-related DLTs will be defined as the following events that occur between Day 1 to Day 7 that are considered possibly, probably, or definitely treatment-related:

- Grade 4 hematologic toxicity.
- Grade 3 hematologic toxicity with exception of transient leukopenia, neutropenia, lymphopenia, thrombocytopenia without bleeding, or anemia lasting 7 days or less.
- Grade 4 non-hematologic toxicities, with exception of asymptomatic increased LDH or lipase or amylase.
- Grade 3 non-hematologic toxicities with exception of nausea, vomiting, diarrhea, or flu-like symptoms that are controlled by optimal supportive management.

Distinguishing clinical manifestations of COVID-19 from treatment-related DLT can be difficult because they can overlap. Manifestations of COVID-19 present at baseline (e.g., fever, shortness of breath) that are unchanged after the study regimen is begun will not be considered DLT. Worsening of these manifestations can be due to COVID-19 or treatment-related, and unless there is a specific well defined unrelated cause, all AEs that are at least possibly related to the study regimen that meet one of the criteria for DLT based on CTCAE severity will be considered DLT.

In patients who received recent chemotherapy, radiation, and/or immunotherapy toxicities from recent chemotherapy would be known to the primary oncologist, and we would interpret AEs attributed to the study regimen with this knowledge in mind. For example, if a patient received cytotoxic chemotherapy known to cause leukopenia prior to development of COVID-19, development of leukopenia following initiation of study therapy will not be considered treatment-related, depending on the expected degree and duration of leukopenia following chemotherapy.

### 10.2.3 Toxicity Management

The toxicity of high dose interferon (20 million units/m²/d) has been established by Kirkwood et al in a number of trials. Most notable was the E1684 trial (47) where HDI (20 million units/m²/d) was administered daily for 5 days x 4weeks. In that trial (n=143), grade 3 toxicities were 67%, grade 4 toxicities were 9% (mainly constitutional and neurologic), and there were 2 treatment related mortalities (grade 5) due to hepatotoxicity. The proportion of Grade 3 and 4 toxicities in that trial were 48.2% for constitutional toxicities (defined as 'worst grade of any constitutional toxicity, including fever, chills, flu-like symptoms, fatigue, malaise, and diaphoresis), and 66% for non-constitutional toxicities (23.8% for myelosuppression, 13.9% for hepatotoxicity, 28% for neurological toxicity).

While the combination of HDI and rintatolimod may lead to synergistic additive side effects, we will monitor subject toxicities for unexpected increases in constitutional symptoms, myelosuppression, hepatotoxicity, and neurological toxicity. We will focus on monitoring for grade 3 or greater treatment related hematologic toxicities, and grade 4 or greater treatment related non-hematologic toxicities. A non-informative prior distribution of SAEs will be utilized to develop the safety stopping rules (details in Section 19).

To our knowledge, the combination of HDI and rintatolimod has not been tested previously in patients with COVID-19. Therefore, we may observe adverse events that were not observed in trials of cancer and specific adverse events may be more severe in patients with COVID-19. One possibility is worsening of acute lung injury or systemic inflammatory response. Though the protocol does not specify specific treatments for such AEs, agents used for cytokine release syndrome, e.g. Tocilizumab, or JAK2, TNFα, IL-1 inhibitors, may be used, based on physician judgment.

- **Gastrointestinal Toxicity**
    - Nausea and/or vomiting should be controlled with adequate antiemetic therapy. Prophylactic antiemetic therapy can be used at the discretion of the investigator/sub-investigator. Subjects are encouraged to take plenty of oral fluids.
    - Diarrhea should be managed with appropriate antidiarrheal therapy. Subjects should be encouraged to take plenty of oral fluids. If symptoms do not decrease to grade 1 or less with adequate antidiarrheal therapy, all protocol drugs should be held until resolved to < grade 1.
- **Pain**
    - For fever or mild local pain, acetaminophen will be used at the discretion of the investigator/sub-investigator or designee.
- **Immunogenicity risk:** Given the limited exposure to interferon alpha-2b (administered on Days 1 and 3), the risk of anti-drug-antibodies is very low. Hypersensitivity reaction can occur (described below). Our plan is to assess all AEs, including immunologic complications, and to provide appropriate management.
- **Hypersensitivity Reactions**

Caution: Subjects who had a mild to moderate hypersensitivity reaction have been successfully re-challenged, but careful attention to prophylaxis and bedside monitoring of vital signs is recommended. Hypersensitivity reactions to interferon alpha-2b and/or rintatolimod will be managed as follows:

- Mild symptoms (e.g., mild flushing, rash, pruritus): Complete infusion. Supervise at bedside. No treatment required.
- Moderate symptoms (e.g., moderate rash, flushing, mild dyspnea, chest discomfort): Stop infusion. Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Resume infusion after recovery of symptoms at a low rate, then, if no further symptoms, at full dose rate until infusion is complete. If symptoms recur, stop infusion. The subject should receive no additional interferon alpha-2b or rintatolimod. Record toxicity.

- Severe life-threatening symptoms (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria): Stop infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. If wheezing is present, that is not responsive to bronchodilators, epinephrine is recommended. Subject should be removed from further protocol therapy. Report as serious adverse event.

### 10.3 General Concomitant Medication and Supportive Care

There are no restrictions on general supportive care, which will be administered based on newest standards of COVID-19 care.

### 10.4 Duration of Study Treatment

A total of 2 daily doses over a 4-day day period of treatment is planned.

The participant may stop treatment earlier than planned in the event that the following occurs:

- Unacceptable toxicity
- Progression to severe COVID-19 infection, defined by new or worse pulmonary infiltrates on Chest X-Ray or CT imaging plus one of the following: room air $Sao_2 \leq 92\%$, room air $PO_2 < 70$ mm Hg, or $PAO_2\text{-}PaO_2 \geq 35$ mm Hg, and/or requiring mechanical ventilation
- Withdrawal of consent from study
- Participant non-compliance with study requirements

## 11 PROCEDURES INVOLVED

Informed consent ***MUST*** be completed prior to receiving any study related procedures.

**To limit exposure of COVID-19 to staff,** patients will be provided with a surgical mask on entry to Roswell Park. The patient will be escorted to the site of drug administration using a dedicated elevator and immediately placed in a room with the door closed. All staff in contact with patients will don PPE. Infusions will be administered in a room with a closed door. History will be obtained by trained staff by phone in advance of study-related visits. Physical exam will be limited to vitals and auscultation of lungs. Following completion of treatment, the patient will be escorted to his/her vehicle by trained staff. A specific SOP will be developed to minimize contact between study subjects and staff and patients.

### 11.1 Screening

Within 3 days prior to treatment initiation and may be the same day as initiation of study treatment:

- Recording of concomitant medications
- Medical and Surgical History
- Physical exam (lung auscultation), Vital Signs and weight; $SaO_2$
- ECOG Performance Status Assessment
- Hematology
- Chemistry
- Arterial blood gas

- Serum HCG pregnancy testing (within 3 days of Day 1 in women of child-bearing potential only)
- EKG
- Chest X-ray or CT imaging (NOTE: If a chest CT is ordered as standard of care prior to starting treatment, a chest x-ray is not required)
- Nasopharyngeal swab
- Evaluations Performed on each day of treatment [(Day 1and Day 3 (+ 1 day)]: Recording of concomitant medications
- Recording of Adverse Events
- Targeted physical exam
    - Auscultation of lungs
    - Vital Signs (temperature, blood pressure, pulse rate and respiratory rate, $SaO_2$) will be performed pre- treatment and at 30 and 60 minutes post rintatolimod (± 5 minutes)
- ECOG Performance Status Assessment
- Hematology
- Chemistry
- Blood (30cc) for correlative studies: On Day 1 treatment and Day 3 treatment, prior to treatment and within 1 hour after end of infusion treatment (two draws on each of these days).
- Nasopharyngeal swabs for viral quantification by quantitative PCR

### 11.2 Follow-up Visits on Days 7 (± 1 day) and 14 (± 3 days)

- Recording of concomitant medications
- Recording of Adverse Events
- Targeted physical exam
    - Lung auscultation and Vital Signs
- ECOG Performance Status
- Hematology
- Chemistry
- Blood (30cc) for correlative studies
- Nasopharyngeal swabs for viral quantification by quantitative PCR

### 11.3 Correlative studies (blood samples)

Three (10 mL) green-top heparinized tubes and one red-top tube of blood will be collected via venipuncture for biomarker analysis at multiple time points (please refer to **Appendix F**: Study Calendar).

Tubes will be labeled with the participant's initials, participant's study number, clinical study number, time of collection and protocol day. Samples will be sent at room temperature to the attention of Laboratory Medicine – Protocol Clinical Research Support (pneumatic Station 19) where they will get accessioned for tracking. Once specimen receipt has been documented, the specimens will be sent at ambient temperature to pneumatic station 641 (located in CCC LOB-4$^{th}$ floor). The Kalinski Laboratory will be notified via telephone *and* e-mail (all contacts to be copied with each e-mail: see contact information below) prior to sample shipment and, the samples will

be held in CSPO until a response is received acknowledging that personnel are available to procure the samples from the pneumatic tube station. Samples will be processed and stored in the Kalinski Laboratory for future analysis.

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Preliminary analyses will include the pre- and post-treatment cytokine levels and immune cell subsets, via RT-PCR, flow cytometry assays, or alternative laboratory methods. . Cytokine measurements will involve ELISAs using validated antibodies and will include generation of a standard curve with known quantities of the analyte and use of appropriate specificity controls, as recommended by the manufacturer. For cryopreserved samples, we will test for batch effects and repeat measurements on 10% of samples over a 3-month period to rule out loss of analyte detection by cryopreservation.

Below is a general description of processing of blood that might be modified per Dr. Puzanov's judgment. Plasma samples are to be separated from whole blood and processed at 4°C using a refrigerated centrifuge at approximately 3000 rpm for 10 minutes with the plasma (0.5 ml aliquots – as many as available) being aliquoted into cryovials per time-point. The samples will immediately be frozen at -70ºC or below until analyzed. PBMCs will then be obtained by Ficoll gradient as per the lab's standard procedure. Two of the tubes will be pooled and the PBMCs will be frozen in Gibco Cell culture freezing media and will be stored in LN2 until time of analysis. The remaining tube of PBMCs will be frozen in RNA later and will be stored in -70 degrees or below until analyzed. Serum will be collected from red top tubes and 0.5 ml aliquots (as many as available) will be frozen at -70ºC. The screw cap polypropylene cryogenic tubes will be labeled with the clinical study number, participant's MR number, participant's study number, protocol time point, protocol day, date and time of draw.

As a component of exploratory aims, blood will be analyzed to assess pre- and post- treatment chemokine and immune cell subsets, via ELISA, RT-PCR, and flow cytometry assays to obtain insights into the synergy between rintatolimod and individual concentrations of IFNα.

In the induction of known mediators of anti-coronavirus responses and factors of intracellular immunity against RNA viral infections in general, we may also evaluate the levels of expression of myxovirus resistance gene (MxA), protein Kinase R (PKR); oligoadenylate synthetase-2 (OAS2); RNAse-L; IFN-stimulated gene-15 (ISG15); IFN-induced proteins with tetratricopeptide repeats (IFIT1) and IFN-inducible transmembrane protein 3 (IFITM3), as well TLR3, RIG-I, MDA5, IRF3, IRF7, in nasopharyngeal swabs material and blood cells of patients on all tiers of treatment, using RT-PCR and, potentially, intracellular protein expression (flow cytometry and image stream).

**Note:** All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

### 11.4 Nasopharyngeal swabs

Nasopharyngeal swabs will be taken for viral quantification by quantitative PCR on:

- Screening: If a potential study participant has already been identified as COVID-19-positive from an outside testing facility, as per current institutional protocol, a nasopharyngeal swab will be obtained for quantitative PCR. Study drug therapy will be initiated within 3 days of screening, including on the same day of screening.
- Each day of treatment (Day 1 and Day 3 (+ 1 day).
- Follow-up Visits on Days 7 and 14

Testing for SARS-CoV-2 will be done upfront and residual samples will be tested for baseline viral load. If there's a problem in supplies, repeat sampling at the indicated time points may not be feasible and will not be considered a protocol deviation.

All samples will be transported to the Molecular Diagnostics facility (Attn: Dr. Jan Nowak) The screening samples will be tested for SARS-CoV-2 as per current institutional protocol; The residual sample left over from clinical testing, as well as from subsequent testing, will be processed by the Molecular Diagnostics facility and the resulting research analytes will be transported to the Kalinski laboratory for storage and analysis (CCC Bldg. 5th Floor, Rm. 502F).

Any remaining RNA may be also analyzed for the markers of antiviral immunity described in the blood correlative studies.

## 12 WITHDRAWAL OF SUBJECTS

### 12.1 Treatment Discontinuation

Upon treatment discontinuation all end of treatment evaluations and tests will be conducted. All participants who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the participant's medical records and the appropriate eCRF.

Reasons for treatment discontinuation should be classified as follows:

- Death
- Toxicity: treatment related or unrelated
- Participant non-compliance with study requirements
- Investigator judgment
    - The Investigator may discontinue a participant if, in his/her judgment, it is in the best interest of the participant to do so.
- Participant voluntary withdrawal

# 13 RISKS TO SUBJECTS

## 13.1 Interferon Alpha-2b

Interferon alpha-2b may cause fever, chills and flu-like symptoms; loss of appetite; nausea; vomiting, diarrhea and abdominal pain; fatigue; lowered white blood count may increase risk of infection; lowered platelets may lead to an increase in bruising or bleeding; hair loss. Other risks which may be common in cases of prolonged administration of interferon alpha-2b include drowsiness; temporary confusion; anxiety, amnesia, irritability, confusion, delusions and depression which can be severe; numbness and/or tingling in the hands and/or feet, skin rashes and inflammation of the pancreas. Inflammation of the pancreas is swelling or irritation of the pancreas which may result in tenderness or pain in the stomach and/or back. When the pancreas is inflamed, the body is not able to absorb all the nutrients it needs.

Additional information on risk is included in the Investigator's Brochure or package insert.

## 13.2 Rintatolimod

Clinical experience with rintatolimod totals over 800 patients with more than 400 patients receiving rintatolimod for at least six (6) months, greater than 200 patients for one (1) year, over 50 patients up to two (2) years, and with 20 or more patients over two (2) years at doses as high as 1200 mg i. v. twice weekly. No evidence of dose-limiting organ toxicity, including hematologic, liver, or renal toxicity, has been observed.

Adverse events related to infusion such as mild flu-like symptoms, transient headache, fever, myalgia, arthralgia, and fatigue/malaise which were seen, usually occur during the initial weeks of treatment and tend to subside on repeated administration. These side events were seen in Chronic Fatigue Syndrome patients, cancer patients, chronic hepatitis B infected patients and individuals infected with HIV at doses of 200 and 400 mg and higher. Patients that experience these minor side effects can continue on rintatolimod and as noted, these signs and symptoms typically subside after several weeks of continued treatment. Specific symptoms of note include a flushing reaction, characterized by at least one occurrence of erythema of the face, neck and chest, which has been observed in approximately 10% of patients treated in various studies. Usually the flushing is both mild and transient and disappears with repeated dosing. Occasionally, it can be accompanied by a tightness of the chest, tachycardia, anxiety, shortness of breath, subjective reports of "feeling hot", diaphoresis and nausea. The reaction is usually infusion-rate dependent and can generally be controlled by slowing the infusion rate. An antihistamine (diphenhydramine hydrochloride) can be helpful in controlling and reducing the response in the occasional patient for whom the symptom persists. Other less frequently occurring adverse effects include nausea, diarrhea, itching, urticaria, bronchospasm, transient hypotension, photophobia, rash, bradycardia, and transient visual disturbances. A severe unexpected local reaction to extravasation of rintatolimod (Ampligen®, Poly I:Poly $C_{12}U$) at the infusion site in the dorsum of the left hand was reported in a Chronic Fatigue Syndrome patient with chilblains. Several patients experienced liver enzyme level elevations while receiving rintatolimod associated with chronic dosing over many weeks.

Rintatolimod has been dosed in combination with alpha interferon in investigator-initiated studies under investigator IND applications during the period between December 1985 and April 1994. A total of 24 patients received combination treatments. Clinical conditions included renal cell carcinoma, chronic myelogenous leukemia, melanoma, and ovarian cancer. Rintatolimod was

given as an IV infusion at a dose of 300 mg twice weekly. The starting dose was sometimes as low as 1-10 mg. The interferons were administered at a dose of 3 million Units daily, with some doses of 0.75 million units at the low side and up to 6 million units at the higher side.

The therapy with rintatolimod in combination with alpha interferon was generally well tolerated without evidence of dose-limiting or cumulative toxicities. The most frequent adverse reactions were considered minor in severity and duration. Most of them were flu-like symptoms such as chills, cold feeling, fatigue, decreased appetite, fever, muscular aches. Also, shortness of breath has been seen as well as hypotension, nausea, anemia, dyspnea, numbness, itching and blurred vision. These adverse events were judged possibly related to the condition of the patients, but also possibly related to the administration of rintatolimod or interferon. In some cases, worsening of the patient's condition has been seen due to tumor progression, but in general favorable clinical patterns were observed in these patients with advanced disease. Such combinations were not intended to be immune modulating and were evaluated in the context of clinical cancer care.

For more risk information, reference the Investigator's Brochure or package insert.

## 14 POTENTIAL BENEFITS TO SUBJECTS

Patients enrolled in this study may demonstrate improved virus control, manifested by reduced symptoms and improved oxygenation or lack of progression of infection to pneumonia and ARDS.

## 15 DATA AND SPECIMEN BANKING

All samples for correlative analysis will be sent to the Kalinski laboratory for processing, storage, and analysis. Samples will be used for planned study assays as well as for future studies that include, but are not limited to, immune responses to viral infections and to immunotherapy.

Any clinical data that is associated with the samples, will be stored on a secure server in the Department of Medicine, will be accessible only by the PI, Co-Investigators and PI designated data manager and, will be password protected. All computer entry and networking programs will be done using PIDs only. Any clinical data and/or specimens for future research will require verification of an IRB-approved protocol and will be de-identified before being released to investigators within and outside of Roswell Park.

**Note:** All investigator or analyzing research laboratories housing research samples need to maintain current Temperature Logs and study-specific Sample Tracking and Shipping Logs. The Principal Investigator/Laboratory Manager must ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

## 16 MEASUREMENT OF EFFECT

### 16.1 Primary Endpoints

- The **primary safety** endpoints are frequency of grade 3 or 4 AEs considered to be possibly, probably, or definitely related to the treatment regimen.
- Evaluate kinetics of viral load in nasopharyngeal swabs based on quantitative PCR in the course of treatment and Days 7, and 14.

### 16.2 Secondary Endpoints

- Clinical efficacy will be assessed by the frequency of these complications: (i) progression of infection requiring hospitalization; (ii) respiratory failure requiring mechanical ventilation (primary efficacy endpoint); and (iii) death within 30 days. If present, acute respiratory distress syndrome (ARDS) will be graded by Berlin criteria (42).
- Kinetics of viral load in the peripheral blood and nasopharyngeal swab based on quantitative PCR in the course of treatment and Days 7 and 14.
- Kinetics of changes of the immune subsets and circulating inflammatory mediators (including CRP, cytokines, chemokines, interferons) in peripheral blood in the course of treatment and at Days 7 and 14.
- Induction of known mediators of antiviral immunity that include (myxovirus resistance gene, MxA; protein Kinase R (PKR); oligoadenylate synthetase-2 (OAS2); RNAse-L, IFN-stimulated gene-15 (ISG15); IFN-induced proteins with tetratricopeptide repeats (IFIT1) and IFN-inducible transmembrane protein 3 (IFITM3), TLR3, RIG-I, MDA5, IRF3, IRF7, in nasopharyngeal swabs material and blood cells of patients on all tiers of treatment. Expression of ACE2 (receptor for SARS-Cov-2 entry) and potentially other genes involved in SARS-CoV-2 infection will be tested in nasopharyngeal samples.

## 17 SAFETY EVALUATION

### 17.1 Adverse Events

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of ‘unrelated’, ‘unlikely’, ‘possible’, ‘probable’, or ‘definite’).

An AE is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

### 17.2 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

### 17.3 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

### 17.4 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated blood potassium level of 7 mEq/L should be recorded as “hyperkalemia”.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

### 17.5 Preexisting Medical Conditions (Baseline Conditions)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

### 17.6 Grading and Reporting Adverse Events

#### 17.6.1 Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 5.0 of the CTCAE is identified and located at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology and documented according to the grading scales provided in the CTCAE Version 5.0.

The relationship of event to study drug will be documented by the Investigator as follows:

**Unrelated:** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.

**Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.

**Possible:** The event follows a reasonable temporal sequence from the time of drug administration but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.

**Probable:** The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions, or concomitant drugs.

**Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

### 17.6.2 Reporting Adverse Events

Routine AEs occurring between the start date of intervention until 30 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

**Guidelines for Routine Adverse Event Reporting for Phase 1 Studies (Regardless of Expectedness)**

| Attribution | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **Unrelated** | X | X | X | X |
| **Unlikely** | X | X | X | X |
| **Possible** | X | X | X | X |
| **Probable** | X | X | X | X |
| **Definite** | X | X | X | X |

**Guidelines for Routine Adverse Event Reporting for Pilot, Phase 2, and Phase 3 Studies (Regardless of Expectedness)**

| Attribution | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **Unrelated** | | | X | X |
| **Unlikely** | | | X | X |
| **Possible** | X | X | X | X |
| **Probable** | X | X | X | X |
| **Definite** | X | X | X | X |

### 17.7 Serious Adverse Events

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in **ANY** of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

#### 17.7.1 Reporting Serious Adverse Events

All new SAEs occurring from the date the participant signs the study consent until 30 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The Roswell Park SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 30 day follow-up period that the investigator determines to be possibly, probably, or definitely related to the study intervention should be reported.

SAEs identified as an Unanticipated Problem by the Investigator must be reported. Please refer to **Section 17.10** for details on reporting Unanticipated Problems.

### 17.8 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

### 17.9 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
    - The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
    - The characteristics of the participant population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed Serious per Section 17.7.

### 17.9.1 Reporting Unanticipated Problems

The Reportable New Information (RNI) Form will be submitted to the CRS Quality Assurance (QA) Office within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS QA Office will submit the RNI to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS QA Office with an updated Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems to the IRB in accordance with their local institutional guidelines.

## 17.10 FDA Reporting

When Roswell Park is the IND holder the following describes the FDA reporting requirements by timeline for AEs and new safety findings that meet the criteria outlined below:

**Within 7 Calendar Days**

Any adverse event that meets ALL the following criteria:

- Related or possibly related to the use of the study drug.
- Unexpected; and
- Fatal or life-threatening.

**Within 15 Calendar Days**

Any adverse event that meets ALL the following criteria:

- Related or possibly related to the use of the study drug.
- Unexpected; and
- Serious but not fatal or life-threatening.

Or, meets ANY of the following criteria:

- A previous adverse event that is not initially deemed reportable but is later found to fit the criteria for reporting (report within 15 days from when event was deemed reportable).
- Any findings from other studies, including epidemiological studies, pooled analysis of multiple studies, or other clinical studies conducted with the study drug that suggest a significant risk in humans exposed to the drug.
- Any findings from animal or in vitro testing that suggest a significant risk for human participants including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.
- Any clinically important increase in the rate of occurrence of a serious, related or possibly related adverse event over that listed in the protocol or investigator brochure.

Sponsors are also required to identify in IND safety reports, all previous reports concerning similar adverse events and to analyze the significance of the current event in the light of the previous reports.

**Reporting Process**

The principal investigator or designee will complete and submit a FDA Form 3500A MedWatch for any event that meets the above criteria. Forms will be submitted to the CRS QA Office via email to CRSQA@RoswellPark.org.

# 18 DATA MANAGEMENT AND CONFIDENTIALITY

## 18.1 Data Collection

Full build studies are managed by Roswell Park CRS Data Management for analysis by Roswell Park Biostatisticians. All electronic case report form (eCRF) data are captured for these studies.

Data management activities are performed using a CTMS system that enables the collection, cleaning and viewing of clinical trial data. CRS data management designs the study-specific database and facilitates development by the Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database is put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs.

## 18.2 Maintenance of Study Documents

Essential documents will be retained per Roswell Park's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with Roswell Park.

## 18.3 Revisions to the Protocol

Roswell Park may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

## 18.4 Termination of the Study

It is agreed that, for reasonable cause, either the Roswell Park Investigators or the Sponsor, may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, Roswell Park may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

# 19 STATISTICAL PLAN

## 19.1 Study Design/Endpoints

This is prospective Phase I/IIa trial basket trial of i.v. rintatolimod administered with or without i.v. IFNα (INTRON® A) in two cohorts of patients: Main Cohort and Expansion Cohort. Only Main Cohort subjects will participate in the Phase I 3+3 portion of this study. The Expansion

Cohort will consist of rintatolimod without IFNα. Neither cohort is randomized. The kinetics of nasopharyngeal viral load will be assessed based on baseline values and on treatment and EOT values. In the Expansion Cohort, the kinetics of nasopharyngeal viral load will be compared with historical controls consisting of Roswell Park patients with COVID-19 of varying severity. All patients will receive best available standard of care in addition to study drug regimens.

**Phase I**. The Phase I component of the protocol consists of a 3+3 design with four dose levels of IFNα (0, 5 MU/M$^2$, 10 MU/M$^2$ and 20 MU/M$^2$ ) and fixed dose rintatolimod (200 mg per day) administered on Days 1 and 3. The sample size for the Phase I trial may range from n=3 to 24.

**Primary Endpoint**

- The primary safety endpoint is the frequency of grade 3 or 4 AEs considered to be possibly, probably, or definitely related to the treatment regimen.

**Phase IIa**. The Phase IIa component of the trial is designed to be a single arm trial of IFNα (at MTD, if reached, otherwise at 20 MU/M$^2$) + rintatolimod along with the best available standard of care. Using each patient's baseline nasopharyngeal viral load, we will evaluate to what extent the study regimen reduces viral load relative historical institutional benchmarks. The sample size will be *n*=10.

**Primary Endpoint**

- Evaluate kinetics of viral load expressed as Ct values in nasopharyngeal swab samples over time measured at baseline (day 0), Days 3 (last day of treatment), 7, and 14 (40). The primary endpoint will be the area under the Ct curve (AUC).

The primary Phase IIa safety endpoint is the frequency of grade 3 or 4 AEs considered to be probably or definitely related to the treatment regimen.

**Secondary Endpoints**

- Clinical efficacy will be assessed by the frequency of these complications: (i) progression of infection requiring hospitalization; (ii) respiratory failure requiring mechanical ventilation; (iii) death within 30 days and (iv) Time to a Ct value of non-detectable.

**Correlative Endpoints**

- Determine the kinetics of changes of the immune subsets and circulating inflammatory mediators (including CRP, cytokines, chemokines, interferons) in peripheral blood in the course of treatment at baseline (Day 0), Days 3, 7, and 14. Plasma and PBMCs will be cryopreserved for future exploratory studies, including the assessment of intracellular signaling and TCR and BCR repertoires as correlates of response to the study regimen.
- Induction of known mediators of antiviral immunity that include (myxovirus resistance gene, MxA; protein Kinase R (PKR); oligoadenylate synthetase-2 (OAS2); RNAse-L, IFN-stimulated gene-15 (ISG15); IFN-induced proteins with tetratricopeptide repeats (IFIT1) and IFN-inducible transmembrane protein 3 (IFITM3), TLR3, RIG-I, MDA5, IRF3, IRF7, in nasopharyngeal swabs material and blood cells of patients on all tiers of treatment. Expression of ACE2 (receptor for SARS-Cov-2 entry) and potentially other genes involved in SARS-CoV-2 infection will be tested in nasopharyngeal samples.

All subjects meeting the eligibility criteria who signed a consent form and receive rintatolimod control will be considered evaluable for efficacy analysis. Safety analysis will be performed on all patients who have signed a consent form and received at least one dose of study medication.

The primary efficacy analysis of the Phase IIa component of the study will be on the intention to treat (ITT) population, which will include all patients who have signed a consent form and undergone randomization, according to the treatment group to which they were allocated.
All data collected will be summarized and presented. Continuous variables will be described as the mean, median, standard deviation, and range of the observations. Categorical data will be described with contingency tables including frequency and percentage. Individual patient listings will be generated and presented.

Statistical descriptions and analyses will be carried out using SAS statistical analysis software version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, USA).

## 19.2 Proposed Data Analysis

### 19.2.1 Safety

SAFETY RUN-IN DESIGN

We will use a 3+3 dose escalation scheme in order to determine the safe dose to utilize in our efficacy analysis. The 3+3 design will consider four dose levels of IFNα (0, 5 MU/M$^2$, 10 MU/M$^2$ and 20 MU/M$^2$) and fixed dose rintatolimod (200 mg per day) administered on Days 1 and 3.

For each cohort, the given dose level will start with three patients, with three patients added to any dose level if we observe 1 out of 3 DLTs. The patients in each cohort will be staggered, so that the first patient in each cohort will have received treatment on Days 1 and 3 before the following patient(s) are enrolled in that cohort. If 2 out of 3 to 6 subjects have a DLT we will not proceed to the next dose level.

### 19.2.2 Efficacy

In order to compare the AUC between rintatolimod versus historical institutional benchmarks we will use the highly efficient approach proposed by Chandrasekhar et al (48). Ct values measured at baseline (Day 0), Days 3, 7 and 14 will be used to measure the AUC using a standard trapezoidal rule where the AUC for the *i*th subject in group *k* (*k*=1 for rintatolimod and *k*=2 for control) as $AUC_{jk} = \sum_{i=1}^{m} c_j Y_{ijk}$ where $t_1 = 0, t_2 = 3,\ t_3 = 7, t_4 = 14, t_5 = 30,$, $m = 5$, the $Y_{ijk}$ 's denote the corresponding Ct values per subject at the respective time points and

$$c_j = \begin{cases} \frac{t_{j+1} - t_j}{2}, j = 1 \\ \frac{t_j - t_{j-1}}{2}, j = m \\ \frac{t_{j+1} - t_{j-1}}{2}, otherwise \end{cases}$$

If a Ct value is >40 it will be considered right censored for the purpose of this analysis, which corresponds to a non-detectable level. We can re-express this formulation using a linear mixed model with details given exactly as in Chandrasekhar et al. (48). A large AUC value for a respective subject is a measure of treatment efficacy as compared to a subject with a lower AUC

value. The primary test of efficacy will be H0: AUC=130 (log2 copies) x day versus H1: AUC>130 (log2 copies) x day.

The secondary clinical efficacy endpoints of (i) progression of infection requiring hospitalization in patients who were not inpatients at study entry; (ii) respiratory failure requiring mechanical ventilation; and (iii) death within 30 days will be compared using Fisher's exact test. Time to a Ct value of non-detectable will be examined using an exact discrete time-to-event Cox model. The analysis of correlative endpoints will be primarily descriptive and graphical in nature.

The primary test of efficacy will be one-sided and tested at level alpha=0.05. All additional tests will be two-sided and tested at level alpha=0.05.

### 19.3 Sample Size Justification

The sample size was based on preliminary data gathered at Roswell Park on patients and employees. The values were similar between the two study groups. The Ct values collected at baseline for n=20 patients and employees had an average of 24.1 log2 copies with a standard deviation of 6.5. The standard deviations after baseline was approximately 4.5 as the Ct values increased. The preliminary estimate for the AUC based on our pilot data is 130 (log2 copies) x day, which is the basis for our null hypothesis. The between time point correlation was estimated to be approximately rho=0.3. Given n=10 subjects we will be able to detect and increase in the AUC to an average of 144 (log2 copies) x day (efficacy) or greater than our assumed institutional benchmark of 130 (log2 copies) x day at power=0.80 and alpha=0.05(one-sided). We simplified this calculation assuming no censoring, which will be accounted for in the final analysis and assumed a compound symmetry covariance structure with the correlation estimate described above.

### 19.4 Randomization

This is a non-randomized trial.

### 19.5 Study Duration and Compliance

All study drug administration and compliance data will be summarized.

### 19.6 Prior and Concomitant Medication

All relevant prior medication and all concomitant medications will be summarized by frequencies and percentages. All medications will be coded using the MeDRA drug dictionary.

### 19.7 Safety Review and Study Suspension

The Roswell Park Data Safety and Monitoring Committee (DSMC) will assess the progress of the study, the safety data, and critical efficacy endpoints. The DSMC will review the study weekly and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design (c) suspension of or, (d) termination of the study.

Additionally, should the study be suspended due to safety; members of the research team, study statistician, and DSMC will meet to discuss safety concerns and possible adjustments to the study or study closure.

Therapy will be discontinued for any Grade 4 treatment-related toxicity.

### 19.8 Procedure for Accounting for Missing, Unused and Spurious Data

Missing data will be indicated in the listings but excluded from all descriptive analyses. All data will be listed, including otherwise unused data. Spurious data will be identified as such, wherever possible.

## 20 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

All Roswell Park Phase I studies are reviewed at the scheduled Early Phase Clinical Trial Committee meetings and the minutes are forwarded to the IRB for review.

In addition, the Roswell Park Data Safety Monitoring Committee will assess the progress of the study, the safety data, and critical efficacy endpoints (Phase I studies will be reviewed quarterly; Phase II, III and pilot investigator-initiated studies will be reviewed semi-annually). The DSMC will review the study and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design (c) suspension of or, (d) termination of the study.

Additionally, should the study be suspended due to safety; members of the research team, study statistician, and DSMC will meet to discuss safety concerns and possible adjustments to the study or study closure.

## 21 VULNERABLE POPULATIONS

The following vulnerable populations will be excluded:

- Chronically cognitively impaired adults (e.g. those with dementia) with impaired decision-making capacity
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

## 22 COMMUNITY-BASED PARTICIPATORY RESEARCH

Not applicable.

## 23 SHARING OF RESULTS WITH SUBJECTS

Individual response data is shared with the participant as a part of their clinical care.

## 24 SETTING

All evaluations and procedures will be conducted on an outpatient basis at Roswell Park Comprehensive Cancer Center.

## 25 PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and

networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

## 26 RESOURCES AVAILABLE

Not applicable.

## 27 PRIOR APPROVALS

Not applicable.

## 28 COMPENSATION FOR RESEARCH-RELATED INJURY

If the subject believes they have been injured as a direct result of their participation in this research study, they will be advised to notify the Roswell Park Patient Advocate at (716) 845-1365 or the Study Doctor at (716) 845-5721.

Medical diagnosis and treatment for the injury will be offered, and a determination will be made regarding appropriate billing for the diagnosis and treatment of the injury. A financial counselor (716-845-3161) will be able to provide an explanation of coverage and to answer questions the subject may have regarding study related billing.

The subject is not prevented from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

## 29 ECONOMIC BURDEN TO SUBJECTS

The participants will not be subject to any economic burden.

## 30 CONSENT PROCESS

The Roswell Park SOP: Informed Consent Process for Research (HRP-090) will be followed.

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

# 31 PROCESS TO DOCUMENT CONSENT IN WRITING

The Roswell Park "SOP: Written Documentation of Consent (HRP-091)" will be followed.

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant or the participant's legally authorized representative in accordance with GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to applicable GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator or designee shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

# 32 DRUGS OR DEVICES

Roswell Park will hold the IND for this study.

## 32.1 Interferon Alpha-2b

Interferon alpha-2b is approved around the world for the treatment of chronic hepatitis C, chronic hepatitis B, hairy cell leukemia, chronic myelogenous leukemia, multiple myeloma, follicular lymphoma, carcinoid tumor, and malignant melanoma. Interferon alpha-2b has many drug classifications including anti-infective, anti-neoplastic, antiproliferative, antiviral and immunological agent.

### 32.1.1 Drug Shipment

Interferon alpha-2b will be provided by Roswell Park and will be ordered from the manufacturer through IDS.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

### 32.1.2 Preparing and Dispensing

The lyophilized product is reconstituted as directed by the manufacturer. Investigational Drug Service Pharmacy (IDS) will prepare and dispense.

For IV injection, it is recommended that interferon alpha-2b be administered as a 100,000 U/mL solution to minimize adsorption of the drug to glass and plastic containers.

### 32.1.3 Drug Administration

Interferon alpha-2b (dose-escalation from 0, 5, 10, and 20 MU/$M^2$ administered as IV over 20 minutes) will be administered intravenously on Day 1 and Day 3 (+ 1 day), as per the standard at Roswell.

### 32.1.4 Drug Storage and Accountability

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility in accordance with the applicable regulatory requirements.

Powder for injection should be stored at 2 to 8°C (36-46°F). After reconstitution, the solution should be used immediately but may be stored up to 24 hours at 2-8°C (36-46°F).

Drug storage temperature will be maintained and recorded, as applicable.

### 32.1.5 Concomitant Medications

Interactions between interferon alpha-2b and other drugs have not been fully evaluated. Caution should be exercised when administering interferon alpha-2b therapy in combination with other potentially myelosuppressive agents. Various medications, such as cytotoxic chemotherapy and immunosuppressive regimens are likely to be discontinued as standard of care in patients with an acute viral infection. However, this protocol will not exclude patients based on recent or continued use of anti-cancer therapy. There is theoretical concern, but not a contraindication, regarding NSAIDs and selective COX-2 inhibitors in patients with COVID-19 infection; these agents won't be offered as part of the study protocol, but are not excluded. Concomitant use of interferon alpha-2b and theophylline decreases theophylline clearance, resulting in a 100% increase in serum theophylline levels. Concomitant interferon alpha-2b and REBETOL® (Ribavirin) use is contraindicated. A more detailed guide concerning drug interactions can be found in **Appendix B**.

## 32.2 Rintatolimod (poly IC analog)

A substituted double stranded poly-ribonucleic acid (polyI:poly$C_{12}U$), rintatolimod preserves activity of poly-IC with a much-improved systemic toxicity profile. The product has been studied extensively for use as a vaccine adjuvant and for its direct antiviral activity, as well in several cancer studies as a monotherapy, but most extensively in chronic fatigue syndrome (CFS).

### 32.2.1 Other names

poly$IC_{12}U$, Ampligen®, poly I: poly$C_{12}U$; Polyinosinic: polycytidylic-polyuridylic acid; polyriboinosinic-polyribocytidylic (uridylic) acid.

### 32.2.2 Formulation and packaging

Rintatolimod is supplied as a liquid solution in glass bottles containing 200 mg (100 mg in case of toxicity) per 80 mL. Rintatolimod is a colorless solution containing 2.5 mg/mL in physiological salts (0.15 M NaCl, 0.01 M phosphate, 0.001 M Mg++). The product does not contain preservatives or antioxidants.

### 32.2.3 Drug Shipment

Rintatolimod will be provided by AIM (previous name: Hemispherx) and shipped to the participating site.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

### 32.2.4 Preparing and Dispensing

A vial of rintatolimod is suitable for direct IV infusion. IDS will prepare and dispense. Each vial should be taken from the refrigerator and allowed to equilibrate to room temperature.

### 32.2.5 Drug administration

Rintatolimod 200 mg will be administered by intravenous infusion after interferon alpha-2b. Additional details on the procedures for receiving, storing and using rintatolimod (Ampligen®) can be found in a separate document entitled "Procedures for Receiving, Storing, and Using Ampligen® (Poly I:Poly $C_{12}U$) Liquid Solution".

The initial administration to start at 20 mL/ hour and increase to 40 mL/ hour after 30 minutes as per the standard at Roswell Total duration of rintatolimod infusion: 2.5 h-3h. Tubing should be flushed with 30 to 50 mL of normal saline solution upon completion. Administration will be followed by 1 hour of observation and vital signs at 30 and 60 minutes post-infusion (± 5 minutes).

### 32.2.6 Drug storage and accountability

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility, as specified by Hemispherx and in accordance with the applicable regulatory requirements.

Rintatolimod should be stored at 2 to 8°C but should be infused at room temperature. Used vials should be accounted for and destroyed according to institutional procedure.

Drug storage temperature will be maintained and recorded, as applicable.

### 32.2.7 Handling and Disposal

The Investigator or designee will be responsible for dispensing and accounting for all investigational drug provided by Hemispherx exercising accepted medical and pharmaceutical practices. Study drugs must be handled as cytotoxic agents and appropriate precautions taken per the institution's environmentally safe handling procedures. All investigational drugs will be dispensed in accordance with the Investigator's prescription or written order.

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. This record will be reviewed by the Sponsor's staff or representative during periodic monitoring visits. It is the Investigator's responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

Used vials (excess drug) will be destroyed according to standard practices after properly accounting for the dispensing. Partially used vials of study drug will not be re-used for other participants.

Under no circumstances will the Investigator supply investigational drug to a third party or allow the investigational drug to be used in a manner other than as directed by this protocol.

In regard to drug receipt, accountability and storage, SOP IDS-601 will be followed

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## 34 APPENDICES/ SUPPLEMENTS

# Appendix A NYHA CLASSIFICATION

## NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

| Class | Functional Capacity | Objective Assessment |
|---|---|---|
| I | Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. | No objective evidence of cardiovascular disease. |
| II | Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. | Objective evidence of minimal cardiovascular disease. |
| III | Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. | Objective evidence of moderately severe cardiovascular disease. |
| IV | Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. | Objective evidence of severe cardiovascular disease. |

## Appendix B DESCRIPTION OF INTRON® A POTENTIAL INTERACTIONS

Aldesleukin: Interferons (Alfa) may enhance the adverse/toxic effect of Aldesleukin. In particular, risks of myocardial and renal toxicity may be increased by this combination. *Risk D: Consider therapy modification*

Methadone: Interferons (Alfa) may increase the serum concentration of Methadone. *Risk C: Monitor therapy*

Ribavirin: Interferons (Alfa) may enhance the adverse/toxic effect of Ribavirin. Hemolytic anemia has been observed. *Risk C: Monitor therapy*

Telbivudine: Interferon Alfa-2b may enhance the adverse/toxic effect of Telbivudine. Specifically, the risk for peripheral neuropathy may be increased. *Risk X: Avoid combination*

Theophylline Derivatives: Interferons may decrease the metabolism of Theophylline Derivatives. **Exceptions:** Dyphylline. *Risk C: Monitor therapy*

Zidovudine: Interferons may enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine. *Risk C: Monitor therapy*

## Appendix C ECOG Performance Status Scores

| Description | Status |
|---|---|
| Fully active, able to carry on all pre-disease performance without restriction. | 0 |
| Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. | 1 |
| Ambulatory and capable of all self-care but unable to carry out any work activities. | 2 |
| Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 3 |
| Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 4 |
| Dead | 5 |

**Appendix D**

**INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM**
**INCLUSION CRITERIA (Main Cohort)**

**Participant Name:** _____

**Medical Record No.:** _____

**Title:** Phase 1/2A Study of Rintatolimod and IFN alpha Regimen in Cancer Patients with COVID-19

Both men and women and members of all races and ethnic groups are eligible for this study.

| **INCLUSION CRITERIA (Main Cohort)** | | | | |
|---|---|---|---|---|
| **Yes** | **No** | **N/A** | **All answers must be "Yes" or "N/A" for participant enrollment.** | **Date** |
| ☐ | ☐ | ☐ | 1. Patients with cancer, with the exception of patients with active acute leukemia and allogeneic hematopoietic stem cell transplant recipients. Patients may be on active therapy or received therapy (e.g., chemotherapy, radiation, or surgery) within 7 years. Patients with active cancer who have not yet been treated (e.g. newly diagnosed cancer or early stage MDS or CLL) are eligible. Basal cell cancer and carcinoma in situ treated with local excision alone do not qualify for inclusion. | |
| ☐ | ☐ | ☐ | 2. Presence of symptomatic infection, defined by fever (T ≥ 38.0 ºC) OR respiratory symptoms (cough, nasal congestion, or shortness of breath), OR lung infiltrates on chest X-ray or CT imaging, Diagnosis of COVID-19 based on PCR testing of respiratory samples. | |
| ☐ | ☐ | ☐ | 3. Age equal to ≥ 18 years or older (children are excluded because COVID-19 typically has a milder course in children, and lack of safety data of this regimen in children). | |
| ☐ | ☐ | ☐ | 4. Laboratory evaluations:<br>o Platelet ≥ 75,000/µL<br>o Hemoglobin ≥ 9 g/dL<br>o Hematocrit ≥ 27%<br>o Absolute Neutrophil Count (ANC) ≥ 1000/µL<br>o Creatinine clearance ≥ 50 mL/min (Cockroft-Gault Equation–note: plasma creatine instead of serum is used at Roswell Park) | |

| INCLUSION CRITERIA (Main Cohort) | | | | |
|---|---|---|---|---|
| **Yes** | **No** | **N/A** | **All answers must be "Yes" or "N/A" for participant enrollment.** | **Date** |
| | | | ○ Total bilirubin ≤ 2 X institutional ULN<br>○ AST (plasma) and ALT(plasma) ≤ 2 X institutional ULN<br>○ Plasma amylase and lipase ≤2 X institutional ULN | |
| ☐ | ☐ | ☐ | 5. In the absence of COVID-19, a life expectancy of at least 6 months is expected. | |
| ☐ | ☐ | ☐ | 6. Participant or health care proxy must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure. | |

**Investigator Signature:** _____ **Date:** _____

**Printed Name of Investigator:** _____

**INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM**
**INCLUSION CRITERIA (Expansion Cohort)**

**Participant Name:** _____

**Medical Record No.:** _____

**Title:** Phase 1/2A Study of Rintatolimod and IFN alpha Regimen in Cancer Patients COVID-19

Both men and women and members of all races and ethnic groups are eligible for this study.

| **INCLUSION CRITERIA (Expansion Cohort)** | | | | |
|---|---|---|---|---|
| **Yes** | **No** | **N/A** | **All answers must be "Yes" or "N/A" for participant enrollment.** | **Date** |
| ☐ | ☐ | ☐ | 1. Patients with cancer or allogeneic stem cell transplant recipients with and without a cancer diagnosis.<br>o Patients with cancer may be on active therapy or received therapy (e.g., chemotherapy, radiation, or surgery) within 7 years.<br>o Patients with active cancer who have not yet been treated (e.g. newly diagnosed cancer or early stage MDS or CLL) are eligible.<br>o Basal cell cancer and carcinoma in situ treated with local excision alone do not qualify for inclusion. | |
| ☐ | ☐ | ☐ | 2. Presence of symptomatic infection, defined by fever (T≥38.0°C ) OR respiratory symptoms (cough, nasal congestion, or shortness of breath), OR lung infiltrates on chest X-ray or CT imaging. Diagnosis of COVID-19 is based on PCR testing of respiratory samples. Severe infection is excluded (see Exclusion Criteria). | |
| ☐ | ☐ | ☐ | 3. Age equal to ≥ 18 years or older (children are excluded because COVID-19 typically has a milder course in children, and lack of safety data of this regimen in children). In the absence of COVID-19, a life expectancy of at least 6 months is expected. | |

| INCLUSION CRITERIA (Expansion Cohort) | | | | |
|---|---|---|---|---|
| **Yes** | **No** | **N/A** | **All answers must be "Yes" or "N/A" for participant enrollment.** | **Date** |
| ☐ | ☐ | ☐ | 4. Participant or health care proxy must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure. There may be specific instances when the patient can't provide informed consent, e.g. they require mechanical ventilation and are sedated, in which case a health care proxy will be able to provide informed consent. Patients with temporary cognitive impairment will be consented once their capacity has returned**.** Patients with chronic cognitive impairment, e.g. dementia, that precludes informed consent will not be enrolled. | |

**Investigator Signature:** _____ **Date:** _____

**Printed Name of Investigator:** _____

**Appendix E**

**INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM**
**EXCLUSION CRITERIA (Main Cohort)**

**Participant Name:** _____

**Medical Record No.:**_____

**Title:** Phase 1/2A Study of Rintatolimod and IFN alpha Regimen in Cancer Patients with COVID-19

| EXCLUSION CRITERIA (Main Cohort) | | | | |
|---|---|---|---|---|
| **Yes** | **No** | **N/A** | **All answers must be "No" or "N/A" for participant enrollment.** | **Date** |
| ☐ | ☐ | ☐ | 1. Patients with severe COVID-19 infection defined by pulmonary infiltrates on Chest X-Ray or CT imaging plus one of the following: room air $SaO_2 \leq 92\%$, room air $PaO_2 < 70$ mm Hg, or $PaO_2$-$PaO_2 \geq 35$ mm Hg. | |
| ☐ | ☐ | ☐ | 2. Contraindication to r-INFα based on prior hypersensitivity, autoimmune hepatitis, decompensated liver disease. | |
| ☐ | ☐ | ☐ | 3. Patients who have active acute myeloid leukemia or acute lymphoid leukemia or are allogeneic hematopoietic stem transplant recipients. Acute leukemia in remission and chronic leukemias are not exclusion criteria. | |
| ☐ | ☐ | ☐ | 4. Cardiac events:<br>a. Acute coronary syndrome, myocardial infarction, or ischemia within past 3 months , or<br>b. New York Heart Association classification of III or IV congestive heart failure (**Appendix A**) | |
| ☐ | ☐ | ☐ | 5. Unwilling or unable to follow protocol requirements. | |
| ☐ | ☐ | ☐ | 6. Patients with known serious mood disorders. | |
| ☐ | ☐ | ☐ | 7. Any additional condition, such as pre-existing inflammatory lung disease, which in the Investigator's opinion deems the participant an unsuitable candidate to receive the study drugs. | |
| ☐ | ☐ | ☐ | 8. Concurrent infections, e.g. bacterial pneumonia, or sepsis, that would make it difficult to evaluate clinical response to therapy or study drug toxicities. | |
| ☐ | ☐ | ☐ | 9. Therapies known to cause cytokine release syndrome (CRS), e.g. engineered T cells, within 30 days. | |
| ☐ | ☐ | ☐ | 10. Patients at high risk for tumor lysis syndrome. | |

| EXCLUSION CRITERIA (Main Cohort) | | | | |
|---|---|---|---|---|
| **Yes** | **No** | **N/A** | **All answers must be "No" or "N/A" for participant enrollment.** | **Date** |
| ☐ | ☐ | ☐ | 11. Concurrent active pneumonitis predating COVID-19, such as from checkpoint inhibitor therapy, chemotherapy-associated toxicity, or radiation pneumonitis. | |
| ☐ | ☐ | ☐ | 12. Autoimmune disease that requires systemic immunosuppression. | |
| ☐ | ☐ | ☐ | 13. Protocol-defined baseline abnormalities in cell counts, renal, or hepatic function. | |
| ☐ | ☐ | ☐ | 14. Any additional condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive the study drugs. | |

**Participant meets all entry criteria:** ☐ **Yes** ☐ **No**

***If "NO", do not enroll participant in study.***

**Investigator Signature:** _____ **Date:** _____

**Printed Name of Investigator:** _____

**INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM**
**EXCLUSION CRITERIA (Expansion Cohort)**

**Participant Name:** _____

**Medical Record No.:**_____

**Title:** Phase 1/2A Study of Rintatolimod and IFN alpha Regimen in Cancer Patients with COVID-19

| **EXCLUSION CRITERIA (Expansion Cohort)** | | | | |
|---|---|---|---|---|
| **Yes** | **No** | **N/A** | **All answers must be "No" or "N/A" for participant enrollment.** | **Date** |
| ☐ | ☐ | ☐ | 1. Patients with respiratory failure requiring mechanical ventilation with FIO2 of > 60%. | |
| ☐ | ☐ | ☐ | 2. Allogeneic hematopoietic stem cell transplant recipients with pulmonary GvHD (any grade) | |
| ☐ | ☐ | ☐ | 3. Cardiac events:<br>a. Acute coronary syndrome, myocardial infarction, or ischemia within past 3 months , or<br>b. New York Heart Association classification of III or IV congestive heart failure (**Appendix A**) | |
| ☐ | ☐ | ☐ | 4. Unwilling or unable to follow protocol requirements. | |
| ☐ | ☐ | ☐ | 5. Any additional condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive the study drugs. | |

**Participant meets all entry criteria:** ☐ **Yes** ☐ **No**

***If "NO", do not enroll participant in study.***

**Investigator Signature:** _____ **Date:** _____

**Printed Name of Investigator:** _____

## Appendix F

## Study Calendar (Main Cohort)

Baseline and/or Screening assessments must be performed within 3 days prior to the first dose of investigational product unless otherwise stated. Therapy may begin on the same day as screening. *If screening and day 1 are completed on the same day, then assessments required on both days may be done only once**. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator.

*If screening and day 1 occur on the same day, correlative blood draw and nasopharyngeal swab collection will be as follows:
Correlative blood draw: In the case when day one of treatment is the same as the screening day, only two blood draws (30 mL each time) are needed for the correlative studies on that day: Before the start of treatment and within 1 hour after the end of the combined infusion (i.e., collect one pre-dose sample and one sample within one hour after end of rintatolimod IV, if screening and Day 1 are the same day).
Nasopharyngeal swabs: In the case when day one of treatment is the same as the screening day, only one nasopharyngeal swab (pre-dose) is required.

| Evaluation | Screening and Informed Consent | Day 1 | Day 3 (+ 1 day) | Day 7 (± 1 day) and Day 14 (± 3 days)[5] |
|---|---|---|---|---|
| Written Informed Consent prior to any Screening Procedures | X | | | |
| Recording of Concomitant Medications | | X | X | X |
| Recording of Adverse Events | | X | X | X |
| Survival Follow-up (through Day 14) | | X | X | X |
| **Clinical Assessments** | | | | |
| Medical & Surgical History | | X | | |

| Evaluation | Screening and Informed Consent | Day 1 | Day 3 (+ 1 day) | Day 7 (± 1 day) and Day 14 (± 3 days)[5] |
|---|---|---|---|---|
| Physical Exam including vital signs[3] | X | X | X | X |
| ECOG Performance Status | X | X | X | X |
| **Laboratory Procedures** | | | | |
| CBC with diff | X | X | X | X |
| CMP | X | X | X | X |
| Serum hCG in women of child-bearing potential | X | | | |
| ABG | X | | | |
| Blood (30cc) for immunologic studies[2] | X | X (prior to treatment) and X (within 1hr after end of infusion treatment) | X (prior to treatment) and X (within 1hr after end of infusion treatment) | X[2a] |
| Nasopharyngeal Swab (as required and based on availability) | X | X | X | X |
| **Imaging/ Other Procedures** | | | | |
| 12-Lead ECG | X | | | |
| CXR or CT scan[4] | X | | | |

| Evaluation | Screening and Informed Consent | Day 1 | Day 3 (+ 1 day) | Day 7 (± 1 day) and Day 14 (± 3 days)[5] |
|---|---|---|---|---|
| Clinical evaluation of endpoints[1] | X | X | X | X |
| **Study Drug Administration** | | | | |
| Rintatolimod/IFN regimen Administration + best available SOC | | X | X | |

1. Hospitalization in patients who were not inpatients at study entry; respiratory failure requiring mechanical ventilation; 14-day survival.
2. Blood (30cc) for correlative studies: On Day 1 and Day 3 prior to treatment and within 1 hour after end of infusion treatment (two draws on each of these days). Note: The combination treatment begins with IV IFNα followed by IV rintatolimod, with the correlative blood draw within 1 hour following IV rintatolimod as indicated above. Refer to Section 11.4. Single draws on the other days.
   2a: Follow-up visits- NOTE: In the event patient cannot tolerate treatment with all 2 days of treatment, then blood (30cc) for correlatives will be collected at time that the patient recovers from toxicities (ideally within 1 week of the last infusion).
3. Physical exam will be limited to vitals and auscultation of lungs. Vital signs (temperature, heart rate, respiratory rate, blood pressure, $SaO_2$), body weight, and height: Height collected at baseline only.
4. NOTE: If a chest CT is ordered as standard of care prior to starting treatment, a chest x-ray is not required.
5. While every effort will be made to complete assessments, there are limitations for outpatients, including securing transport to Roswell Park. Some follow up visits will need to be done virtually, and in other cases, may be limited to viral swabs. These missed assessments or sample collections for outpatients will not be considered protocol violations.

**Study Calendar (Expansion Basket: Rintatolimod)**

| Evaluation | Screening and Informed Consent | Day 1 | Day 3 (or Day 4)[5] | Day 7 (± 1 day) and Day 14 (± 3 days) and Day 30 (± 3 days)[6,7] |
|---|---|---|---|---|
| Written Informed Consent prior to any Screening Procedures | X | | | |
| Recording of Concomitant Medications | | X | X | X |
| Recording of Adverse Events | | X | X | X |
| Survival Follow-up (through Day 14) | | X | X | X |
| **Clinical Assessments** | | | | |
| Medical & Surgical History | | X | | |
| Physical Exam including vital signs[3] | X | X | X | X |
| ECOG Performance Status | X | X | X | X |
| **Laboratory Procedures** | | | | |
| CBC with diff | X | X | X | X |
| CMP | X | X | X | X |
| Serum hCG in women of child-bearing potential | X | | | |

| Evaluation | Screening and Informed Consent | Day 1 | Day 3 (or Day 4)[5] | Day 7 (± 1 day) and Day 14 (± 3 days) and Day 30 (± 3 days)[6,7] |
|---|---|---|---|---|
| ABG | X | | | |
| Blood (30cc) for immunologic studies[2] | X | X (prior to treatment) and X (within 1hr after end of infusion treatment) | X | X[2a] |
| Nasopharyngeal Swab (as required and based on availability) | X | X | X | X |
| **Imaging/ Other Procedures** | | | | |
| 12-Lead ECG | X | | | |
| CXR or CT scan[4] | X | | | |
| Clinical evaluation of endpoints[1] | X | X | X | X |
| **Study Drug Administration** | | | | |
| Rintatolimod Administration + best available SOC | | X | X | X[6] |

1. Hospitalization in patients who were not inpatients at study entry; respiratory failure requiring mechanical ventilation; 15-day survival.
2. Blood (30cc) for correlative studies: On Day 1 prior to treatment and within 1 hour after end of infusion treatment (two draws on Day 1). Note: The treatment begins with IV rintatolimod, with the correlative blood draw within 1 hour following IV rintatolimod as indicated above. Refer to Section 11.4.

2a: Follow-up visits- NOTE: In the event patient cannot tolerate treatment, then blood (30cc) for correlatives will be collected at time that the patient recovers from toxicities (ideally within 1 week of the infusion).

3. Physical exam will be limited to vitals and auscultation of lungs. Vital signs (temperature, heart rate, respiratory rate, blood pressure, $SaO_2$), body weight, and height: Height collected at baseline only.
4. NOTE: If a chest CT is ordered as standard of care prior to starting treatment, a chest x-ray is not required.
5. Based on the PI's judgment, additional infusions of rintatolimod at 200 mg may be administered 3 to 4 days apart, after the Day 3 (or Day 4) administration. Decisions about additional rintatolimod infusions will be based on evaluation of AEs attributed to rintatolimod, particularly increased FIO2 needs. Patients who do not receive additional rintatolimod infusions will follow the above schedule for EOT/Follow-up visit.
6. Based on the PI's judgment, additional infusions of rintatolimod at 200 mg may be administered 3 to 4 days apart. Decisions about additional rintatolimod infusions will be based on evaluation of AEs attributed to rintatolimod, particularly increased FIO2 needs. A maximum of 12 rintatolimod infusions may be administered per patient.
7. While every effort will be made to complete assessments, there are limitations for outpatients, including securing transport to Roswell Park. Some follow up visits will need to be done virtually, and in other cases, may be limited to viral swabs. These missed assessments or sample collections for outpatients will not be considered protocol violations.