abbvie

pharmacyclics
An AbbVie Company

Protocol for Study M20-310 (PCYC-1150-IM)

ibrutiNib in SARS CoV-2 induced Pulmonary Injury and Respiratory failure (iNSPIRE)

VERSION:	3.0	DATE:	06 July 2020
SPONSOR:	AbbVie Inc.*	NUMBER OF SITES:	Approximately 8-12
ABBVIE INVESTIGATIONAL PRODUCT:	Ibrutinib	EudraCT:	Not applicable

FULL TITLE: ibrutiNib in SARS CoV-2 induced Pulmonary Injury and Respiratory failure (iNSPIRE)

Incorporating Versions 1.0, 2.0, 3.0, and Administrative Change 1

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

SPONSOR/EMERGENCY MEDICAL CONTACT:*

[redacted]
AbbVie Inc.
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

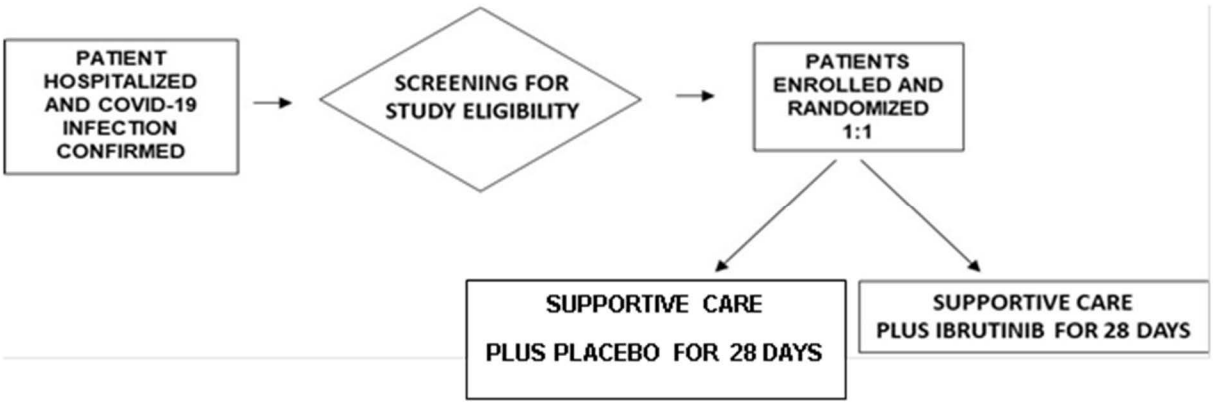
Office:
Mobile:
Email: [redacted]

EMERGENCY 24-hour Number: +1 973-784-6402

*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

SCHEMA



No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

abbvie

pharmacyclics
An AbbVie Company

TABLE OF CONTENTS

CONFIDENTIAL INFORMATION
No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

LIST OF TABLES

CONFIDENTIAL INFORMATION
No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

LIST OF FIGURES

LIST OF APPENDICES

CONFIDENTIAL INFORMATION
No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

1 OBJECTIVES

1.1 Study Design

There is currently no standard of care for hospitalized patients experiencing coronavirus disease 2019 (COVID-19) infections beyond supportive care. Numerous studies examining various study interventions are underway. Discovering/providing treatment options for patients with moderate or severe COVID-19 infection is a high priority, particularly for those with respiratory distress. Exaggerated cytokine response triggered by Alveolar Type II cells and resident macrophages in response to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) appears etiological for the pulmonary injury and respiratory failure associated with COVID-19 infection. Ibrutinib blocks Toll-receptor signaling, and cytokines associated with SARS-CoV-2, including those found in Alveolar Type II (ACE2+) cells. Importantly, in a relevant experimental mouse model, ibrutinib protected mice subjected to lethal intranasal inoculums of mouse adapted H1N1 influenza and suppressed inflammatory cell recruitment and pathological cytokines that overlapped with many of those observed in SARS-CoV-2 infected patients. Based on this, it is hypothesized that Ibrutinib may potentially provide protection against lung injury. Ibrutinib is an oral agent approved by the United States (US) Food and Drug Administration (FDA), European Medicines Agency, and other global health authorities for the treatment of various B-cell malignancies. For those patients whose health care providers feel that they qualify to participate in this study, who meet inclusion/exclusion criteria and sign an associated consent form, they will be enrolled and randomized 1:1 in a randomized, placebo-controlled, double blinded study to receive either supportive care and placebo **or** supportive care and ibrutinib for up to 28 days. For subjects randomized to receive ibrutinib, the dose of ibrutinib will be 420 mg a day. Approximately 46 subjects will be enrolled in this study. Participating clinical sites must have the capability of implementing appropriate infection control measures to prevent infection of study staff and others who share the clinical site space.

1.2 Primary Objective

The primary objective of this study will be:

- To evaluate the proportion of subjects alive and without respiratory failure at Day 28

1.3 Secondary Objectives

The secondary objectives of this study will be:

- To determine if the addition of ibrutinib to supportive care reduces necessity for hospitalization, length of need for supplemental oxygen, mechanical ventilation in hospitalized subjects who presented with COVID-19 related pulmonary distress requiring supplemental oxygen.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

- To assess the safety and tolerability of ibrutinib as an adjuvant therapy to supportive care in hospitalized subjects who presented with COVID-19 related pulmonary distress requiring supplemental oxygen.

2 BACKGROUND

2.1 Study Disease(s)

Subjects with confirmed COVID-19 infection by reverse transcriptase (RT)-polymerase chain reaction (PCR) from nasopharyngeal swabs, who requires hospitalization and has been on supplemental oxygen for a duration of ≤ 5 days for pulmonary distress related to COVID-19 infection are eligible for this study.

2.2 IND Agent

Ibrutinib is an irreversible inhibitor of Bruton's Tyrosine Kinase (BTK) that is approved by the US. FDA for the treatment of adult subjects with:

- Mantle cell lymphoma (MCL) who have received at least 1 prior therapy.
  - Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL).
- CLL/SLL with 17p deletion
- Waldenström's macroglobulinemia (WM).
- Marginal zone lymphoma (MZL) who require systemic therapy and have received at least 1 prior anti-CD20-based therapy.
  - Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- Chronic graft versus host disease (cGVHD) after failure of 1 or more lines of systemic therapy.

2.3 Rationale

COVID-19 is an infectious disease caused by SARS-CoV-2.[1] Pulmonary failure is the main cause of mortality related to COVID-19 infection.[2,3] Up to 80% of patients who require hospitalization for COVID-19 infection require supplemental oxygenation for an average of 13 days.[4] Furthermore 30 - 40% of those hospitalized for pulmonary distress may require mechanical ventilation.[2,5] Therapies that block COVID-19 related lung injury and improve pulmonary function are therefore urgently needed.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

SARS-CoV-2 binds via the ACE2 -receptor that is highly expressed on ACE2+ cells in the lung.[6] ACE2+ cells constitute 5 - 15% of the lung epithelium. While Alveolar Type I cells are highly adapted for gas exchange, ACE2+ cells have a specialized role in innate immune response.[7] ACE2+ cells express Toll-like receptors (TLRs) and can trigger inflammatory cytokines and chemo-attractants in response to viral and bacterial pathogens that recruit and activate other immune cells including macrophages and neutrophils.[8-12] Highly relevant to coronavirus infection, expression of pro-inflammatory and chemo-attractant cytokines interleukin (IL)1-B, IL6, interferon-inducible protein 10 (IP10/CXCL10), monocyte chemoattractant protein-1 (MCP-1/CCL2), and tumor necrosis factor alpha (TNF-a) were identified in the ACE2+ cells from autopsy tissue of SARS-CoV-1 infected patients, that appeared causally related to the acute lung injury and pathogenesis observed with SARS-CoV-1 (Figure 1).[13] A similar profile of elevated cytokine levels of IL6, IL8, IP10/CXCL10 and MCP-1 was also reported in the plasma of SARS-CoV-1 patients during the progressive and end stage of infection,[14] a profile more consistent with M1 polarized macrophage response (Figure 2).[15,16]

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Figure 1. A Model for the Immunopathogenesis of SARS Based on SARS-Cov-1 Model

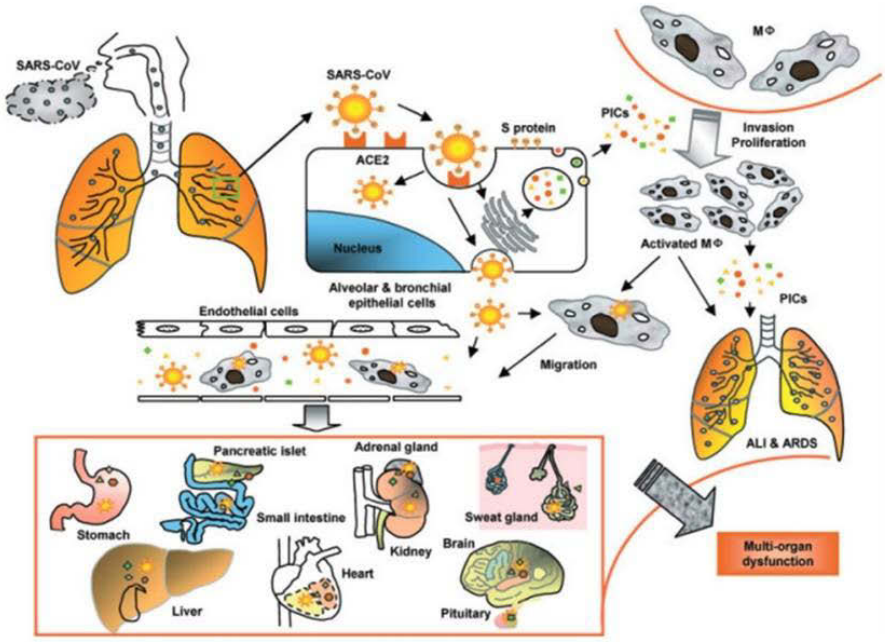
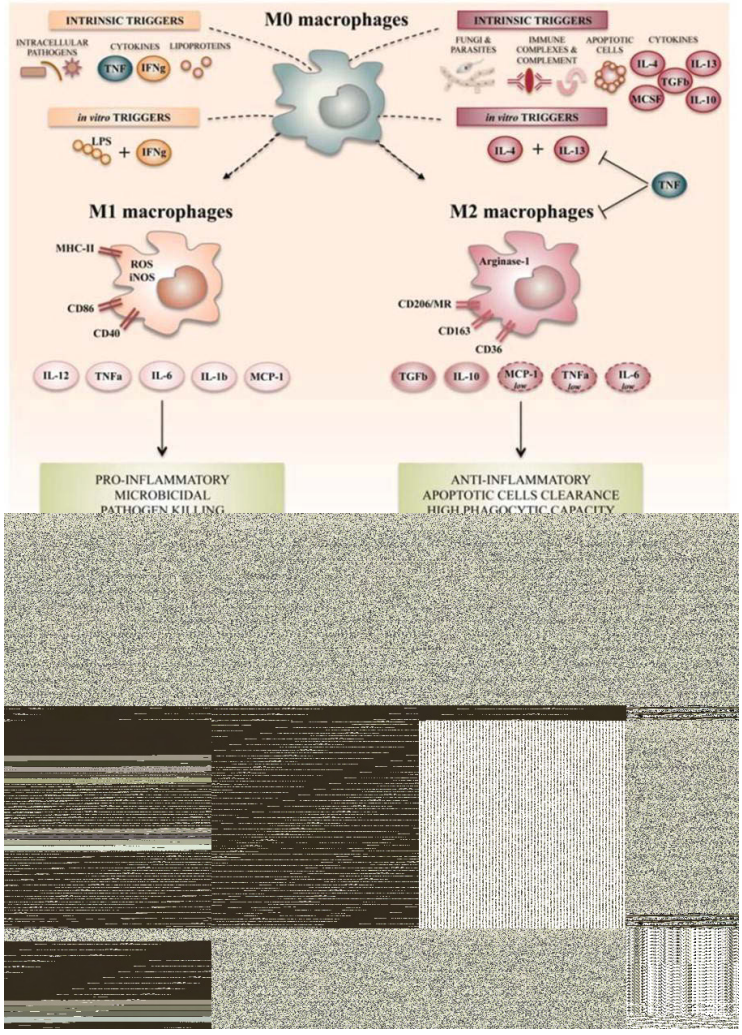


Figure 1. A model for the immunopathogenesis of SARS based on SARS-Cov-1 model. SARS-CoV in droplets enters into the lung, where the virus binds via its S protein to ACE2 on the alveolar or bronchial epithelial cells. The virus replicates in these cells, from which new virions are released into the blood. The infected cells under the stimulation of SARS-CoV and some uninfected cells induced by viral antigens or PIC-regulatory factors produce high levels of PICs to mediate inflammatory responses for combating the virus. However, these PICs also damage the host cells. Some of the PICs, eg monocyte chemoattractant protein-1 (MCP-1), attract monocytes in blood to migrate to the alveolar cavities, where the monocytes are stimulated by other PICs to become proliferative and/or activated macrophages (MO). The activated macrophages can produce more PICs and may transmit SARS-CoV to other sites. Some of the PICs, including TGF-β1 and TNF-α, may induce apoptotic death of the epithelial cells, pneumocytes, and lymphocytes, or mediate pulmonary fibronosis, resulting in ALI and ARDS. The cell-free and MO-associated SARS-CoV in the blood can be transmitted from the lung to other organs to infect the ACE2-expressing cells in the local sites. More PICs are produced and the level of PICs in the blood is rapidly elevated, leading to multi-organ dysfunction. MO = macrophages; ALI = acute lung injury; PICs = pro-inflammatory cytokines. Figure and Legend taken from Het al, 2006.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Figure 2. Summary of the Main Macrophage Polarization States of Activated Macrophages



SARS-CoV-1 shares 86% homology and has a similar pathogenetic mechanism to SARS-CoV-2.[17,18] Similar to SARS-CoV-1 patients, SARS-Cov-2 patients that required intensive care showed elevated plasma levels of inflammatory cytokines and chemo-attractants such as IL2, IL6, IL7, IL10, granulocyte colony stimulating factor (G-CSF), IP-10/CXCL-10, MCP-1/CCL2, macrophage inflammatory protein (MIP)-1a/CCL3, and TNF-a.[19] The importance of inflammatory cytokines to lung injury in SARS-CoV-2 infected patients has been suggested by reports of benefit with IL6 and IL6-receptor blocking antibodies, and clinical trials to examine their use have been initiated (NCT04317092, NCT04306705, NCT04315298).

In previous studies, we and others showed an important role for the TEC family member BTK, and its upstream activator, hematopoietic cell kinase (HCK), a SRC family member in triggering TLR-mediated signaling.[20-22] Both BTK and HCK can be triggered by MYD88, a TLR-adaptor protein that signals for all Toll receptors except TLR3 in response to viral and bacterial pathogens, including coronaviruses.[23] ATII

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

cells express TLRs, as do alveolar macrophages that coordinate inflammatory responses with ATII cells.[8-12] As components of TLR/MYD88 signaling, BTK and HCK can drive inflammatory cytokine production through ERK1/2.[24]

In a transgenic mouse model, overexpression of activated HCK promoted extensive pulmonary inflammation and enhanced innate immune response characterized by extensive eosinophilic and mononuclear cell infiltration within the lung parenchyma, alveolar airspaces, and around blood vessels, as well as marked epithelial mucus metaplasia in conducting airways.[25] Lungs from these mice show areas of emphysema and pulmonary fibrosis, which together with inflammation resulted in altered lung function and respiratory distress, particularly in aging mice.[25] Elevated levels of TNF-a were also identified in the bronchoalveolar lavage fluids of these mice following lipopolysaccharide (LPS) challenge. The pulmonary pathology findings from these mice show great overlap with those described in the lungs of patients with COVID-19 infection which showed serous and fibrin exudation with alveolar infiltration consisting majorly of macrophages and monocytes. The blood vessels of alveolar septum were also congested, edematous and widened, with modest infiltration of monocytes and lymphocytes.[26,27]

Ibrutinib is a highly potent, covalent inhibitor of BTK (biochemical IC_{50} 0.5 nM). Ibrutinib is also a potent reversible inhibitor of HCK (IC_{50} 49 nM).[22,28] The IC_{50} levels for BTK and HCK are well within the pharmacologically attainable dosimetry of orally administered ibrutinib, although HCK inhibition has not yet been demonstrated in patients under ibrutinib therapy, possibly due to the rapid clearance.[29] Serially collected blood samples from patients with CLL, WM, and cGVHD on ibrutinib monotherapy showed marked reductions in pro-inflammatory and chemo-attractant cytokines that greatly overlapped with those reported elevated in the plasma of SARS-Cov-1 and SARS-COV-2 patients, and in ACE2+ cells from lung tissue of SARS-CoV-1 patients (Table 1).[13,14,19,30-32] In the iLLUMINATE randomized study, CLL subjects treated with ibrutinib immediately prior to infusion with obinutuzumab also showed significantly decreased levels of inflammatory cytokines associated with infusion related reactions (a cytokine release syndrome).[33]

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Table 1. Summary of Pro-Inflammatory and Chemo-Attractant Cytokine Patterns

	HE[13]	JIANG[14]	HUANG[19]	NIEMANN[30]	GREIL[33]	VOS[31]	MIKLOS[32]
PATIENTS	CoV-1	CoV-1	CoV-2	CLL ON IBRUTINIB	CLL ON IBRUTINIB	WM ON IBRUTINIB	cGVHD ON IBRUTINIB
TISSUE	ACE2+ cells	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
GMCSF			↑				↓
IL1B	↑						
IL2			↑				↓ (IL2RA)
IL6	↑	↑		↓	↓	↓	
IL7			↑				
IL8		↑		↓	↓	↓	↓
IL10			↑	↓	↓	Variable	
IP10/CXCL10		↑	↑	↓		↓	↓
MCP-1/CCL2	↑	↑	↑	↓	↓		↓
MIP-1A/CCL3			↑	↓			↓
MIP1B/CCL4			↑	↓		↓	↓
TNFA	↑			↓	↓	↓	↓

cGVHD = chronic graft versus host disease; CLL = chronic lymphocytic leukemia; CoV = coronavirus; GM-CSF = granulocyte macrophage colony stimulating factor; IL = interleukin; SARS = severe acute respiratory syndrome; TNF = tumor necrosis factor; WM = Waldenstrom's macroglobulinemia

Note: red highlight indicates patients infected with SARS-CoV-1 and SARS-CoV-2; green highlight indicates following ibrutinib treatment in patients with CLL, WM, and cGVHD.

The potential for ibrutinib to abrogate lung injury and death was demonstrated in an experimental model wherein mice challenged with a lethal intranasal inoculum of a mouse adapted strain of H1N1 influenza virus were protected against lung injury. Control mice that received phosphate buffered saline (PBS) developed respiratory failure, along with histological and computed tomography (CT) findings consistent with lung injury in sharp contrast to the mice that received ibrutinib (Figure 3).[34]

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Figure 3. Pulmonary Findings for Mice Treated with Phosphate Buffered Saline or Ibrutinib Following Lethal Intranasal Challenge with Mouse-Adapted H1N1 Influenza

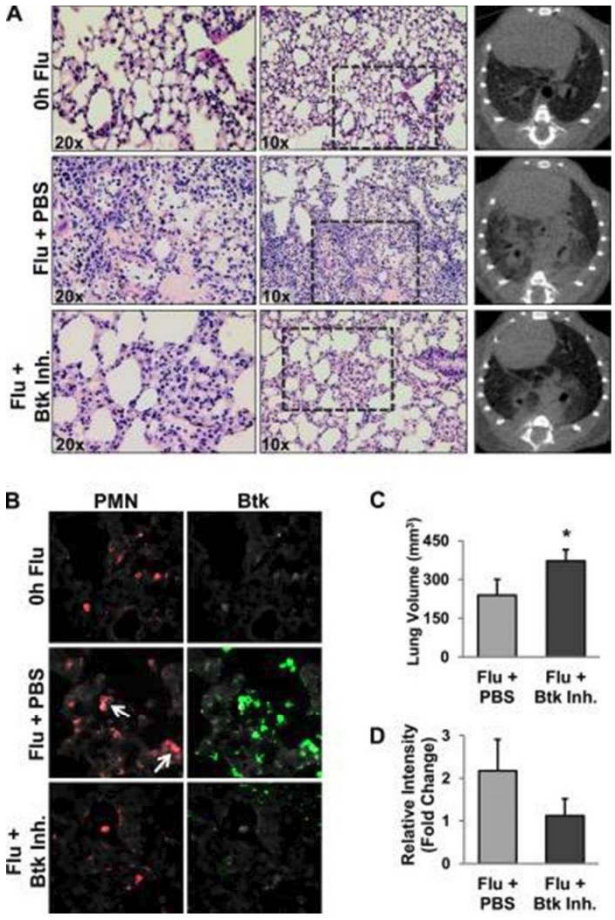


Figure 3. Pulmonary findings for mice treated with PBS or ibrutinib following lethal intranasal challenge with mouse dapted H1N1 influenza. Figure A: representative hematoxylin-eosin-stained lung sections (left and middle) and CT images (right) from mice 7 days after influenza A virus (Flu) infection [n = 10 and 5 mice for PBS- and Btk inhibitor (Inh)-treated groups, respectively]. B: representative images of Bruton's tyrosine kinase (Btk) in lungs of influenza A virus-infected mice. Tissue sections were analyzed by immunofluorescent staining for Btk and a PMN marker (Ly6G 1A8). White arrows indicate Ly6G/Btk double-positive cells; note differences in Btk staining between PBS- and Btk inhibitor-treated groups. C: lung volume derived from CT data (n = 10 and 5 mice for PBS- and Btk inhibitor-treated groups, respectively). Values are means ± SD; n = 3 mice in each group. *P < 0.05 (by Mann-Whitney rank sum test). D: average intensity of Btk staining expressed as fold change over control. Values are means ± SD; n = 3 mice in each group. Figures and legend taken from Florence et al, 2018.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Mice treated with PBS also lost weight and died, whereas those treated with ibrutinib recovered their weight after a brief loss and all survived (Figure 4).[34] Notably, mice treated with ibrutinib also showed decreased inflammatory cell infiltration as well as pro-inflammatory cytokines in lung tissues that included pro-inflammatory and chemo-attractant cytokines such as IL1β, IL6, KC/CXCL1, TNF-a, and MCP-1 observed in SARS-Cov-1 and SARS-CoV-2 patients (Figure 5).[34]

Figure 4. Survival and Weight Loss of C57BL/6 Mice Infected Intranasally with Influenza A Virus

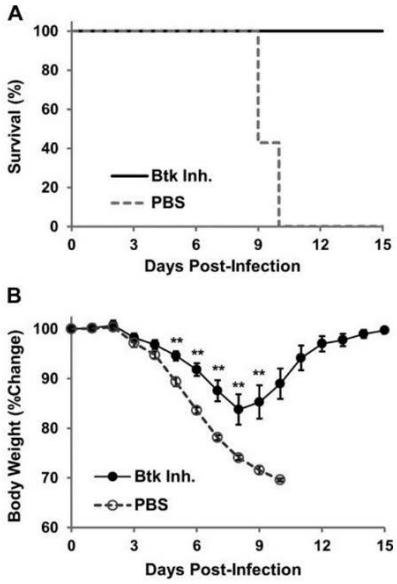


Figure 4. Survival (*A*) and weight loss (*B*) of C57BL/6 mice infected intranasally with influenza A virus (A/PR/8/34). Starting 3 days after infection, mice were treated daily with PBS ($n = 7$) or Bruton's tyrosine kinase (Btk) inhibitor (Inh, $n = 10$) administered intranasally. Animals were monitored until death (4 mice) or weight loss of >30%, at which point they were euthanized and counted as dead (3 mice). Values for weight loss are means ± SE. Statistical significance of weight loss for *days 4–9* of PBS-treated mice ($n = 7$) and Btk inhibitor-treated mice ($n = 10$) was determined by 2-way repeated-measures ANOVA with post hoc Bonferroni's *t*-test: $^{**}P < 0.01$. Figure and legend taken from Florence et al, 2018.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Figure 5. Inflammatory Cells Observed in BAL Fluids and Cytokine Levels from Lung Homogenates in Mice Treated with Phosphate Buffered Saline or Ibrutinib Following Lethal Intranasal Challenge with Mouse-Adapted H1N1 Influenza

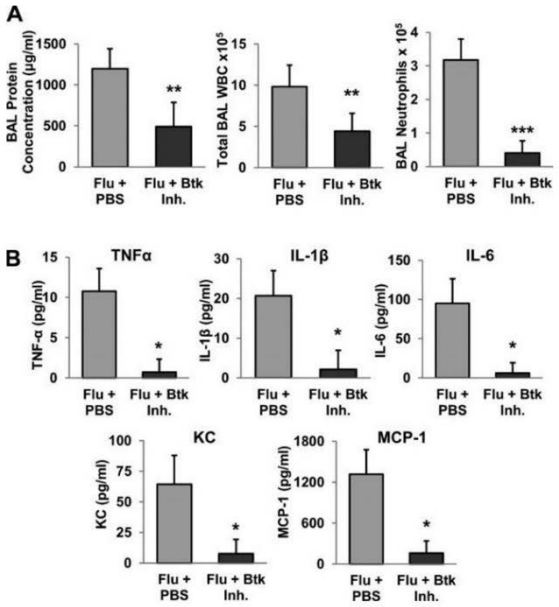


Figure 5. Inflammatory cells observed in BAL fluids, and Cytokine Levels from Lung Homogenates in mice treated with PBS or ibrutinib following lethal intranasal challenge with mouse-adapted H1N1 influenza.Bronchoalveolar lavage (BAL) protein concentration, total white blood cell (WBC) count, and number of neutrophils in BAL fluids at 7 days after influenza A virus (Flu) infection. Values are means ± SD; n = 10 and 4 mice for PBS- and Bruton's tyrosine kinase (Btk) inhibitor (Inh)-treated groups, respectively, for BAL protein concentration and 10 and 5 mice for PBS- and Btk inhibitor-treated groups, respectively, for cell counts. $^{**}P < 0.01$ (by Mann-Whitney rank sum test); $^{***}P < 0.001$ (by Student's t-test). B: inflammatory cytokine/chemokine concentrations in lung homogenates from mice at 7 days after influenza A virus infection. Values are means ± SD; n = 10 and 5 mice for PBS- and Btk inhibitor-treated groups, respectively. $^{*}P < 0.001$ (by Student's t-test). Figures and legend taken from Florence et al, 2018.

The above findings support the rationale that an exaggerated cytokine response triggered by Alveolar Type II cells and resident macrophages in response to SARS-CoV-2 is etiological for the pulmonary injury and respiratory failure associated with COVID-19 infection. The importance of inflammatory cytokines to lung injury in SARS-CoV-2 infected patients has been suggested by reports of benefit with IL6 and IL6-receptor blocking antibodies, and clinical trials to examine their use have been initiated (NCT04317092, NCT04306705, NCT04315298). The ability to block inflammatory cytokine production to limit pulmonary injury has been observed in patients with severe COVID-19 infections who received treatment with the IL6 blocking antibody Tocilizumab.

Ibrutinib blocks Toll-receptor signaling, and cytokines associated with SARS-CoV-2, including those found in Alveolar Type II (ACE2+) cells. Importantly, in a relevant experimental mouse model, ibrutinib protected mice subjected to lethal intranasal inoculums of mouse adapted H1N1 influenza and suppressed inflammatory cell recruitment and pathological cytokines that overlapped with many of

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

those observed in SARS-CoV-2 infected patients. Ibrutinib may therefore protect against lung injury in patients with COVID-19 related pulmonary distress.

A case series of 6 patients being treated with ibrutinib for WM were recently published, which suggests that ibrutinib may protect against pulmonary injury in COVID-19 infected patients.[35] Five of the 6 patients were on the recommended dose of 420 mg/day, while the sixth patient was on a reduced dose of 140 mg/day due to arthralgias. The 5 patients on ibrutinib at 420 mg/day did not experience dyspnea and did not require hospitalization. Their clinical course was marked by steady improvement, with resolution or near resolution of COVID-19 related symptoms. The 1 patient on the reduced dose of 140 mg/day experience progressive dyspnea and hypoxia resulting in hospitalization. Ibrutinib dosing was held upon hospital admission due to findings of bilateral ground glass opacities and a pleural effusion on chest CT. Hydroxychloroquine (HCQ) and azithromycin were administered, however azithromycin was discontinued on hospital Day 3 due to QRS complex tachyarrhythmia. Hypoxia worsened and fever persisted during HCQ. Ibrutinib was restarted at 140 mg/day and tocilizumab 400 mg on hospital Day 5 with improvement in oxygenation and reduction in C-reactive protein (CRP). Intravenous immunoglobulin was administered on hospital Days 6 - 10, with worsening hypoxia and increased CRP noted on hospital Day 10, and which required mechanical ventilation. Given the lack of hypoxia in the other COVID-19 infected WM patients on full dose ibrutinib, the dose of ibrutinib was increased from 140 mg/day to 420 mg/day on hospital Day 11 and 12. On hospital Day 12, the patient had a rapid improvement in oxygenation followed by successful extubation and maintenance of oxygen saturation of 94 - 96% on 3 liters/min supplemental oxygen by nasal cannula. The patient continued to improve, with oxygen saturation of 95% on room air and further decrease in CRP on Day 14, then was discharged home. The authors suggest that ibrutinib may provide protection against lung injury and improve pulmonary function in hypoxic patients with COVID-19 due to the aforementioned modulation of inflammatory and chemo-attractants cytokines.

3 PARTICIPANT SELECTION

3.1 Eligibility Criteria

Inclusion Criteria

- 1. Age $\geq$ 18 years
- 2. Willing and able to provide informed consent prior to study therapy, including by virtual consenting per hospital policy.
- 3. Subject requires hospitalization for COVID-19 infection
- 4. Subject has Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)-2 infection confirmed by RT-PCR test before study entry.
- 5. Subject requires supplemental oxygen for pulmonary distress related to COVID-19 infection, has been on supplemental oxygen for no more than 5 days, and on breathing room air has oxygen saturation levels of 94% or less.
- 6. Subject has radiographic evidence of pulmonary infiltrates.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

- 7. Females of childbearing potential (FCBP) must use 1 reliable form of contraception or have complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) while participating in the study; and 2) for at least 1 month after discontinuation of study drug. FCBP must be referred to a qualified provider of contraceptive methods if needed. FCBP must have a negative serum pregnancy test as of screening.
- 8. Men must agree to use a latex condom during treatment and for up to 3 months after the last dose of ibrutinib during sexual contact with a FCBP.
- 9. Adequate hematologic function defined as:
  - Absolute neutrophil count (ANC) > 750 cells/mm^3 (0.75×10^9/L)
  - Platelet count > 50,000 cells/mm^3 (50×10^9/L)
  - Absolute lymphocyte count (ALC) > 500 cells/mm^3
- 10. Adequate hepatic and renal function defined as:
  - Estimated creatinine clearance (CrCl) ≥ 30 mL/min (Cockcroft-Gault).
  - Bilirubin < 2.0 × ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin).
- 11. Must be within 10 days of confirmed diagnosis of COVID-19.

Key Exclusion Criteria

- 1. Respiratory failure at time of screening as defined per protocol with any of these following therapies:
  - Endotracheal intubation and mechanical ventilation
  - ECMO
  - High flow nasal cannula oxygen at flow rates ≥30 L/min and fraction of delivered oxygen ≥ 0.5 (Subjects are eligible if utilizing oxygen delivered by high-flow nasal cannula at flow rates < 30 L/min or fraction of delivered oxygen < 0.5)
  - Non-invasive positive pressure ventilation
- 2. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
- 3. On a BTK-inhibitor, anti-IL6, anti-IL6R, or Janus kinase inhibitor (JAKi).
- 4. Has received rituximab within 180 days from study entry.
- 5. Known bleeding disorders (e.g., von Willebrand's disease or hemophilia).
- 6. Major surgery within 4 weeks of study entry.
- 7. Subjects in whom surgery is anticipated to be necessary within 72 hours.
- 8. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

- 9. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen (HBsAg), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
- 10. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.
- 11. Asymptomatic arrythmias (e.g., NSVT, bradycardia HR less < 50, or AV block, or any other atrial or ventricular arrythmia) and or history of ejection fraction < 40% on an echo.
- 12. Subjects receiving a strong cytochrome P450 (CYP) 3A4 inhibitor with the exception of those receiving anti-fungal therapy/prophylaxis (Appendix C).
- 13. Subjects with chronic liver disease and hepatic impairment meeting Child Pugh class C (Appendix E). Note that clinical or laboratory changes attributed to acute liver dysfunction are not applicable to the evaluation of the Child-Pugh classification.
- 14. Female subjects who are pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 1 month of last dose of study drug. Male subjects who plan to father a child while enrolled in this study or within 3 months after the last dose of study drug.
- 15. Unwilling or unable to participate in all required study evaluations and procedures.
- 16. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).
- 17. Vaccinated with a live, attenuated vaccine within 4 weeks.
- 18. Uncontrolled hypertension (systolic blood pressure > 150 mm Hg).
- 19. History of interstitial lung disease.
- 20. Subjects on therapeutic anticoagulation at baseline.
- 21. Subject has history of malignancies, except:
    - Malignancy treated with curative intent and with no evidence of active disease present for more than 1 year prior to Screening and felt to be at low risk for recurrence by treating physician.
    - Subjects managed with localized radiation or hormonal therapy.
    - Adequately treated non-melanoma skin cancer or lentigo maligna without current evidence of disease.
    - Adequately treated cervical carcinoma in situ without current evidence of disease.
- 22. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3.0 × ULN, and total bilirubin > 2.0 × ULN.
- 23. International normalized ratio (INR) ≥ 1.5 × ULN attributable to coagulation disorders.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

- 24. Subject is co-enrolled in another interventional trial.

3.2 Inclusion of Women and Minorities

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

4 REGISTRATION

Participants will be registered and randomly assigned to their treatment arm as per procedures outlined in a separate document.

5 TREATMENT PLAN

Subjects will be enrolled and randomized 1:1 in a randomized, placebo-controlled, double blinded study to receive either supportive care and placebo **or** supportive care and ibrutinib for up to 28 days. For subjects randomized to receive ibrutinib, the dose of ibrutinib will be 420 mg a day. Approximately 46 subjects will be enrolled in this study. Treatment for subjects on ibrutinib may be stopped at the discretion of the treating physician after 14 days if the subject is clinically stable and has been off supplemental oxygen for > 48 hours.

Nasogastric tube administration of ibrutinib is permitted for subjects unable to take ibrutinib/placebo orally (see Pharmacy Manual for guidance). Dose de-escalation for toxicity is permitted (see Section 6). Subjects may receive any supportive care treatments and/or interventions, however, infection prophylaxis-particularly for subjects receiving steroids, and dose modifications for cytochrome P450 (CYP) 3A inhibitors may be necessary (see Table 2 in Section 5.4 and Appendix C). See also Table 4 for administration of ibrutinib to subjects with chronic hepatic impairment. Drug guidance for dose modifications of ibrutinib related to agents that may be in use to treat COVID-19 infection are also provided in Appendix D**.** If subject is on chloroquine or hydroxychloroquine frequent electrocardiogram (EKG) or telemetry monitoring should be performed to monitor QT interval changes for subjects on ibrutinib/placebo.

Administration of ibrutinib/placebo therapy and dosing should be recorded in the subject's medical record. A diary will be provided for discharged subjects to record daily dosing as outpatients.

5.1 Treatment Criteria

Treatment should be withheld for adverse events (AE) as outlined below:

- Grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic and/or antidiarrheal therapy) related to ibrutinib.
- Grade 4 or unmanageable nonhematologic Grade 3 toxicities related to ibrutinib
- Neutrophil count ≤ 500/µL

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

- In subjects without baseline thrombocytopenia:
  - Platelet count ≤ 50,000/µL in the presence of bleeding
  - Platelet count ≤ 25,000 µL without bleeding

For AEs that are felt to be related to worsening COVID-19 infection, the investigator may continue ibrutinib, however, in subjects with hepatic or cardiac dysfunction, bleeding, or multiple infections related to COVID-19 infection, the risks of continuing ibrutinib may outweigh the potential benefit of continuing treatment with ibrutinib.

5.2 Agent Administration

Ibrutinib or placebo will be administered orally once daily. Three capsules (each 140 mg) of ibrutinib or placebo are to be taken around the same time each day with a glass of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. For subjects who require nasogastric tube (NGT) placement while on study, capsules may be administered by opening the capsules, mixing with water, and flushing down the NGT (see Pharmacy Manual for details). Though the use of strong CYP3A inhibitors/inducers (see Appendix C), and grapefruit and Seville oranges should be avoided for the duration of treatment, treatment with antifungal prophylaxis (e.g., voriconazole, posaconazole) is permitted; however, dose reductions are necessary (see Section 5.4). See also Table 4 for administration of study drug to subjects with chronic hepatic impairment. If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

Subjects will be treated for up to 28 days. Treatment may be stopped at the discretion of the treating physician after 14 days if the subject is clinically stable and has been off supplemental oxygen for > 48 hours. The dose of 420 mg/day of ibrutinib is the dose approved by the FDA for the treatment of subjects with CLL, WM, and cGVHD. Subjects with these disorders receive ibrutinib until disease progression or prohibitive side effects which cannot be managed with dose reduction. The dose chosen reflects daily dosing associated with reduced inflammatory and chemo-attractant cytokines observed in CLL, WM, and cGVHD subjects that are elevated in subjects with SARS-CoV-1 and SARS-CoV-2 infections and may be responsible for pulmonary injury (see Section 2.3).

Dose reductions for toxicity will be permitted (see Section 6).

For hospitalized subjects, study drug will be administered by nursing staff. For subjects discharged from the hospital, study drug will be self-administered, and participants will be instructed to write in a diary daily, documenting that the drug was taken and AEs experienced. Subjects should be instructed to take the study drug with a glass of water at approximately the same time each day. Subjects taking study drug at home will be instructed on how to complete the diary by study staff prior to discharge. If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose. The missed dose will not be made up and must be returned at the next scheduled visit. The subject will be instructed to document missed drug doses in the study diary. Furthermore, they will

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

be instructed to call their provider, the site or principal investigator if vomiting occurs or they have recurrence of their COVID-19 symptoms or any other AEs consistent with the product label. If the pills are vomited, this should be noted on the subject diary, but a replacement dose should not be taken that day. All dosages prescribed and dispensed to the subject, and all dose changes during the study should be recorded. Diaries will be collected at the end of the treatment period. In the event of circumstances that prevent a discharged subject from returning to clinic, a tele-health visit is permitted. Study staff will collect or coordinate with subject in the event of a tele-health visit for the return of any unused drug and the study diary. Unused drug will be counted and returned to the pharmacy to be destroyed. A prescription for dispensing study drug for at home use, as detailed above, will be filled by the study pharmacy. Medication labels will comply with US legal requirements and be printed in English. The storage conditions for study drug will be described on the medication label. Study drug will be provided by Pharmacyclics LLC/AbbVie Inc. Ibrutinib or placebo is formulated as capsules for oral administration and will be available for this study in 140 mg and 70 mg capsules.

Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose. There is no specific experience in the management of ibrutinib overdose in subjects. There are limited data on the effects of ibrutinib overdose. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1,400 mg/day). In a separate study 1 healthy subject who received a dose of 1,680 mg experienced reversible Grade 4 hepatic enzyme increases (AST and ALT). Refer to the IB for additional details about this case. There is no specific antidote to ibrutinib. Subjects who ingest more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

5.3 General Concomitant Medication and Supportive Care Guidelines for Subjects on Study Drug

Supportive care medications and intervention for COVID-19 infection, including use of a ventilator support as clinically indicated is permitted at the treating physician's discretion. Drug guidance for dose modifications of study drug related to agents that may be in use to treat COVID-19 infection are also provided in Appendix D.

Careful monitoring for signs and symptoms of bleeding are indicated, consistent with the safety profile of ibrutinib. Anti-emetics are permitted if clinically indicated. All concomitant medications during the treatment period should be recorded. The following restrictions apply during the entire duration of the study:

- If steroids are necessary, strongly consider treatment with an appropriate anti-fungal prophylaxis agent (e.g., voriconazole/posaconazole). Consider the addition of anti-bacterial prophylaxis as clinically necessary.
- Concomitant use of hydroxychloroquine or chloroquine should be avoided if possible.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

- Growth factors (i.e., G-CSF, GM-CSF, erythropoietin, platelets growth factors etc.) and transfusion support is permitted.
- Concomitant use of anti-platelet agents and anticoagulants should be avoided (if possible) due to the anti-platelet effects of ibrutinib, however their use may be clinically necessary.
- The use of deep vein thrombosis prophylaxis is permitted. Participants receiving anti-platelet agents in conjunction with study drug should be observed closely for any signs of bleeding or bruising, and study drug should be withheld in the event of any Grade 2 or higher bleeding events until ≤ Grade 1. Participants with any grade central nervous system bleeding should have treatment discontinued.
- Subjects requiring the initiation of therapeutic anticoagulation therapy (e.g., atrial fibrillation), consider the risks and benefits of continuing study drug treatment. If therapeutic anticoagulation is clinically indicated, treatment with study drug should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.
- Supplements such as fish oils and vitamin E preparations should be avoided.
- Use study drug with caution in subjects requiring other anticoagulants or medications that inhibit platelet function.
- Subjects with a history of hepatitis B and C viral infection and baseline negative PCR that develop elevations in liver function tests should be evaluated for viral reactivation.
- Subjects cannot co-enroll in other interventional trials. Other interventions are acceptable, including remdesivir, and open-label compassionate use of therapies, such as convalescent plasma.

5.4 Medications to be Used with Caution

5.4.1 CYP3A Enzyme Inhibitors/Inducers

Ibrutinib is primarily metabolized by CYP3A4. Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure, and strong CYP3A inhibitors should be avoided. Avoid grapefruit and Seville oranges during study drug administration as these contain moderate inhibitors of CYP3A. Dose adjustment of study drug due to concomitant use of CYP3A inhibitors should follow Table 2 as applicable.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Table 2. Ibrutinib Dose Modification Guidance for Co-Administration with CYP3A Inhibitors

Co-administered Drug	Recommended Ibrutinib or Placebo Dose for the Duration of the Inhibitor Use[a]
Mild CYP3A inhibitors	420 mg once daily. No dose adjustment required.
Moderate CYP3A inhibitors	280 mg once daily.
Voriconazole 200 mg twice daily Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	140 mg once daily.
Posaconazole at higher doses[b]	70 mg once daily.
Other strong CYP3A inhibitors	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential. If these inhibitors will be used short-term (such as anti-infectives for 7 days or less), interrupt ibrutinib. If the benefit outweighs the risk and long-term dosing is required (more than 7 days), reduce ibrutinib dose to 140 mg once daily for the duration of the inhibitor use.

CYP3A = cytochrome P450 isoform 3A; IV = intravenous

a. Monitor for adverse reactions and interrupt or modify dose as recommended (see Dosage and Administration).

b. Posaconazole at higher doses (posaconazole suspension 200 mg three times daily or 400 mg twice daily, posaconazole IV injection 300 mg once daily, posaconazole delayed-release tablets 300 mg once daily).

A list of common CYP3A inhibitors and inducers is provided in Appendix C**.** For further information, please refer to the current version of the ibrutinib IB and examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/.

This website is continually revised and should be checked frequently for updates.

5.4.2 Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp) nor other major transporters, except organic cation transporter 2 (OCT2). The dihydrodiol metabolite and other metabolites are P-gp substrates. Ibrutinib is a mild inhibitor of P-gp and breast cancer resistance protein (BCRP). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose. There is no clinical data available. To minimize a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin or methotrexate, should be taken at least 6 hours before or after ibrutinib. Ibrutinib may also inhibit BCRP systemically and increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Antiplatelet Agents and Anticoagulants

Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed. Supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib. Bleeding events of any grade, including bruising and petechiae, occurred in subjects treated with ibrutinib. See below for guidance on management of subjects to reduce risk of bleeding while on ibrutinib and requiring surgeries or procedures. Subjects with congenital bleeding diathesis have not been studied.

5.5 Guidelines for Ibrutinib Management with Surgeries or Procedures

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be considered in the perioperative period for subjects on study drug who require surgical intervention or an invasive procedure.

5.5.1 Minor Surgical Procedures

For minor procedures (e.g., central venous catheter, arterial line placement) that are urgently needed and could result in bleeding, immediately stop study drug and consider transfusion with platelets just prior to procedure. Study drug should be held for 24 hours after procedure. If there is ongoing bleeding after the procedure, additional platelet transfusions can be administered and ibrutinib held to 24 hours after bleeding stops. No drug hold or platelet transfusions are needed for routine venipunctures or peripheral intravenous line placement.

For subjects requiring endotracheal intubation, study drug should be temporarily stopped for 24 hours following intubation. If there is evidence of bleeding at the time of the endotracheal intubation, a platelet transfusion should be given as soon as possible. If there is no evidence of bleeding during intubation, study drug may be resumed after 24 hours.

For subjects who require endotracheal intubation after enrollment on the trial, study drug may be continued if, in the opinion of the investigator, the subject appears to be benefiting from treatment and the risk of continuing therapy outweighs the risks associated with ibrutinib (e.g., bleeding).

5.5.2 Elective Major Surgical Procedures

For any elective surgery or invasive procedure requiring sutures or staples for closure, study drug should be held at least 3 - 7 days prior to the intervention (except for emergency procedures) and should be held at least 3 - 7 days after the procedure and restarted at the discretion of the treating physician when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes. For less than 7 days hold prior to the procedure, consider a transfusion of platelets just prior to the procedure to decrease risk of bleeding.

5.5.3 Emergency Major Surgery Procedures

For emergency procedures that could result in bleeding, and require sutures or staples for closure, subject unblinding will be permitted. For subjects on ibrutinib arm, transfusion with platelets prior to

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

the procedure should be given and study drug held after the procedure for at least 3 days after the surgical procedure. Consider also additional platelet transfusions peri- and post-operatively to reduce bleeding risk or active bleeding.

5.6 Duration of Therapy

Duration of therapy will depend on individual response, evidence of pulmonary disease progression and tolerance. In the absence of treatment delays due to AEs, treatment may continue until 1 of the following criteria applies:

- Intercurrent illness that in the medical judgment of the treating physician prevents further administration of treatment.
- Unacceptable AEs.
- Subject demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements.
- Subject decides to withdraw from the protocol therapy.
- General or specific changes in the participant's condition, including the development of atrial fibrillation that render the participant unacceptable for further treatment with study drug in the judgment of the treating physician.
- Study drug should be stopped in subjects experiencing Grade 4 toxicity, and not resumed. These subjects should be followed through to toxicity resolution to at least Grade 2 or less and study completion.
- Treatment for subjects on ibrutinib may be stopped at the discretion of the treating physician after 14 days if the subject is clinically stable and has been off supplemental oxygen for > 48 hours.
- For all subjects discontinuing from study treatment, the reason for discontinuation should be recorded in the medical record.

Subjects will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the medical record. Alternative care options will be discussed with the participant.

5.7 Duration of Follow Up

Participants will be followed for 8 weeks following start of therapy or until death, whichever occurs first. Subjects experiencing grade 4 toxicities at least possibly related to study drug will be followed until toxicity resolution to at least Grade 2 or less. Participants removed from protocol therapy for unacceptable AEs will be followed until resolution or stabilization of the AE.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Pregnancy
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the electronic case report form (eCRF) In addition, subjects who are lost to follow-up or withdraw consent must be reported to AbbVie immediately so they can potentially be replaced.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified), the investigator is responsible for notifying independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

6 DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using above. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, antidiarrheals, etc.). All AEs experienced by subjects that at least may be possibly related to ibrutinib will be collected from the time of the first dose of study treatment, through the end of therapy should be documented in the medical record. If subjects continue to experience ibrutinib toxicity at the end of treatment, they may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible. Dose de-escalations for toxicity will be performed per Table 3.

Dosing will be held for any of the following conditions:

- Grade 4 ANC (< 500/µL). Discontinue study drug. Neutrophil growth factors may be used for ANC recovery.
- Grade 3 Platelets (< 50,000/µL) in the presence of clinically significant bleeding events; or

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

- Grade 4 Platelets (< 25,000/µL). Discontinue study drug. Platelet transfusions may be used for platelet recovery.
- Grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic and/or antidiarrheal therapy); discontinue study drug for grade 4 nausea, vomiting or diarrhea.
- Any other grade 4 toxicities and any unmanageable non-hematologic Grade 3 or higher toxicities. Discontinue study drug.
- For Grade 3 atrial fibrillation, consider the risks and benefits of restarting and continuing study drug. If clinically indicated, the use of non-warfarin or vitamin k antagonist anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation. Discontinue study drug for Grade 4 atrial fibrillation.

For subjects experiencing treatment emergent Grade 3 toxicities (e.g., ALT or AST > 5 × ULN) related to study drug, hold study drug. Treatment may be restarted if toxicity resolves to baseline at the next lowest dose level per Table 3**.**

Table 3. Dose De-Escalation Schedule for Toxicity

Dose Level	Study Drug
Level 1 – Starting Dose	420 mg/day (Days 1 - 28)
Level 2	280 mg/day
Level 3	140 mg/day
Level 4	Discontinue

For AEs that are felt to be related to worsening COVID-19 infection, the investigator may continue study drug, however, in subjects with worsening hepatic or cardiac dysfunction, bleeding, or multiple infections related to COVID-19 infection, study drug should be discontinued.

Any subject developing the following laboratory abnormalities should permanently discontinue study treatment:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and (total bilirubin ≥ 2 × ULN or INR > 1.5)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right
- Upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

For subjects with mild chronic liver impairment (Child-Pugh Class A), the recommended dose is 140 mg daily. For subjects with moderate chronic liver impairment (Child-Pugh Class B), the recommended dose is 70 mg daily. Monitor subjects for signs of ibrutinib toxicity. It is not recommended to administer ibrutinib to subjects with severe hepatic impairment. Subjects with clinically significant chronic hepatic

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

impairment at the time of Screening (Child- Pugh Class C) are excluded from study participation. Concomitant use of strong CYP inhibitors is not permitted in subjects with chronic hepatic impairment. Refer to Appendix E for Child-Pugh classification. Please refer to Table 4 for dose modifications due to chronic hepatic impairment.

Table 4. Dose Modification Guidance for Chronic Hepatic Impaired Subjects

	Child Pugh Class A (Mild hepatic impairment)*		**Child Pugh Class B (Moderate hepatic impairment)**		**Child Pugh Class C (Severe hepatic impairment)**
	Ongoing at time of enrollment	Develops during study	Ongoing at time of enrollment	Develops during study	Develops during study
Ibrutinib Dose (daily)	140 mg	1. Hold study drug until improvement to baseline. 2 Restart dose at 140 mg 3. Discontinue for recurrence	70 mg	1. Hold study drug until improvement to baseline. 2. Restart dose at 70 mg 3. Discontinue for recurrence	Discontinue study drug

* In the event that additional reduction is needed, ibrutinib should be held for non-hepatic toxicity until resolution.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore 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 the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from study drug, necessitate therapeutic medical intervention, meets protocol-specific criteria (Section 5.1 and Section 6), and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If any of the following SAE or AEs are reported, then the following supplemental report must be completed.

Serious Adverse Event or Adverse Event	Supplemental Report
Cardiac events Myocardial infarction or unstable angina Heart failure Cerebral vascular accident and transient ischemic attack Cardiovascular procedures (SAE Supplemental Procedure eCRF)	MACE eCRF
Discontinuation or interruption of study drug due to a hepatic-related AE A hepatic-related SAE ALT/AST > 8 × ULN or ALT/AST > 3 × ULN with a total bilirubin > 2 × ULN	Hepatic AE eCRF

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eCRF = electronic case report form; MACE = major adverse cardiovascular events; SAE = serious adverse event; ULN = upper limit of normal

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (as appropriate) as a SAE within 24 hours of the site being made aware of the SAE:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event.

All AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an IMP related to any dose administered that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, or are a congenital anomaly or birth defect.
SUSAR	A suspected SAR: refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is not listed is the applicable Reference Safety Information, and meets 1 of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. All individually reported SARs are considered suspected.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE according to the NCI CTCAE Version 5.0.

The investigator will use the following definitions to assess the relationship of the AE to the use of the study drug (ibrutinib/matching placebo):

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.8). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through 90 days following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

7.1 Adverse Event List for Ibrutinib

7.1.1 Risks

Bleeding-related events

There have been reports of hemorrhagic events in subjects treated with ibrutinib both with and without thrombocytopenia. These include primarily minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib. Monitor for signs and symptoms of bleeding. Supplements such as fish oil and vitamin E preparations should be avoided. Subjects with congenital bleeding diathesis have not been studied. See Section 5.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 5.5 for guidance on ibrutinib management with surgeries or procedures.

CONFIDENTIAL INFORMATION
No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Cardiac Arrhythmias

Atrial fibrillation, atrial flutter, and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Periodically monitor subjects clinically for cardiac arrhythmia. Subjects who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest discomfort or new onset of dyspnea) should be evaluated clinically, and if indicated, have an EKG performed. For cardiac arrhythmias which persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines.

Hypertension

Hypertension has occurred in subjects treated with ibrutinib. Regularly monitor blood pressure in subjects treated with ibrutinib and initiate or adjust antihypertensive medication throughout treatment with ibrutinib as appropriate.

Cerebrovascular Accidents

Although causality has not been established, cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of ibrutinib in the post-marketing setting, with and without concomitant atrial fibrillation and/or hypertension. Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) have been reported in subjects treated with ibrutinib.

Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged, follow the protocol dose modification guidelines (see Section 6).

Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections. Although causality has not been established, cases of progressive multifocal leukoencephalopathy and hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Non-Melanoma Skin Cancer

Non-melanoma skin cancers have occurred in subjects treated with ibrutinib. Monitor subjects for the appearance of non-melanoma skin cancer.

Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been rarely reported in subjects treated with ibrutinib. It may be difficult to separate from those of COVID-19. Monitor subjects for pulmonary symptoms indicative of ILD, and if suspected to be ibrutinib related, discontinue therapy. If symptoms develop, interrupt ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines.

Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested. A female subject must immediately inform their treating physician if she becomes pregnant from the time of consent to 30 days after the last dose of ibrutinib. A male subject must immediately inform the treating physician if his partner becomes pregnant from the time of consent to 90 days after the last dose of ibrutinib. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue ibrutinib. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus. Although pregnancy itself is not regarded as an AE, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days (or 90 days for male partners) after the last dose of study drug must be reported. Any occurrence of pregnancy must be reported to AbbVie Pharmacovigilance, or designee, per SAE reporting timelines. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing will need to be reported to AbbVie Pharmacovigilance per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol specified follow-up periods including post-progression follow-up for overall survival. If observed, enter data in the corresponding eCRF.

Table 5: Treatment-Emergent Adverse Events Reported by Subjects Receiving Ibrutinib Monotherapy (Safety Population)

	Subjects Receiving Ibrutinib Monotherapy (N=1600)		
	TEAEs in >10% of Subjects[a]	TEAEs related to Ibrutinib in >5% of Subjects	Grade 3 or 4 TEAEs in >2% of subjects[a]
Subject with 1 or more events	1581 (98.8%)	1382 (86.4%)	1132 (70.8%)
Preferred Term			
Diarrhoea	733 (45.8%)	512 (32.0%)	62 (3.9%)
Fatigue	553 (34.6%)	281 (17.6%)	59 (3.7%)
Cough	419 (26.2%)	91 (5.7%)	NA
Nausea	402 (25.1%)	225 (14.1%)	NA
Upper respiratory tract infection	366 (22.9%)	92 (5.8%)	NA
Anaemia	352 (22.0%)	163 (10.2%)	118 (7.4%)
Pyrexia	352 (22.0%)	101 (6.3%)	NA
Neutropenia	305 (19.1%)	229 (14.3%)	245 (15.3%)
Oedema peripheral	301 (18.8%)	NA	NA
Thrombocytopenia	285 (17.8%)	182 (11.4%)	122 (7.6%)
Muscle spasms	279 (17.4%)	144 (9.0%)	NA
Arthralgia	272 (17.0%)	114 (7.1%)	NA
Constipation	268 (16.8%)	87 (5.4%)	NA
Vomiting	233 (14.6%)	85 (5.3%)	NA
Headache	232 (14.5%)	NA	NA
Decreased appetite	230 (14.4%)	101 (6.3%)	NA
Pneumonia	227 (14.2%)	98 (6.1%)	148 (9.3%)
Hypertension	220 (13.8%)	NA	87 (5.4%)
Dyspnoea	217 (13.6%)	NA	NA
Back pain	202 (12.6%)	NA	NA
Urinary tract infection	197 (12.3%)	NA	39 (2.4%)
Sinusitis	191 (11.9%)	NA	NA
Rash	188 (11.8%)	118 (7.4%)	NA
Abdominal pain	186 (11.6%)	NA	34 (2.1%)
Contusion	181 (11.3%)	NA	NA
Dizziness	178 (11.1%)	NA	NA
Atrial fibrillation	NA	NA	58 (3.6%)
Cellulitis	NA	NA	38 (2.4%)
Febrile neutropenia	NA	NA	47 (2.9%)
Hypokalaemia	NA	NA	39 (2.4%)
Hyponatraemia	NA	NA	48 (3.0%)
Increased tendency to bruise	NA	90 (5.6%)	NA
Neutrophil count decreased	NA	NA	53 (3.3%)
Platelet count decreased	NA	87 (5.4%)	NA
Stomatitis	NA	85 (5.3%)	NA

Monotherapy studies include: 54179060CLL1017, 54179060LEU1001, PCI-32765-JPN-101, PCI-32765CLL3002, PCI-32765FLR2002, PCI-32765LYM1003, PCI-32765MCL2001, PCI-32765MCL2002, PCI-32765MCL3001, PCYC-04753, PCYC-1102-CA, PCYC-1104-CA, PCYC-1106-CA, PCYC-1111-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, PCYC-1118E-CA, PCYC-1121-CA, PCYC-1127-CA Arm C, PCYC-1131-CA Cohort 1.

[a] Regardless of causality.

Note: Adverse events are presented by descending frequency of PT within TEAEs in >10% of Subject, those with the same frequency are presented alphabetically.

NA: AEs that do not meet the criteria.

Adverse Events were coded using MedDRA Version 22.0

[TSFAE25.RTF] [JNJ-54179060\Z_IB\DBR_IB2019\RE_IB2019\PROD\TSFAE25.SAS] 20NOV2019, 18:08

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

7.2 Expedited Adverse Event Reporting

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

For safety concerns, contact the Virology and General Medicine Safety Team at:

Virology and General Medicine Safety Team Dept.
1 North Waukegan Road AP51-3
North Chicago, Illinois 60064
Office: +0001 847-938-1870
Email: SafetyManagement_Virology@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted]
AbbVie Inc.
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Office: [redacted]
Mobile:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Therapeutic Area Medical Director:

HOTLINE: +1 (973) 784-6402

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

8 PHARMACEUTICAL INFORMATION

8.1 Ibrutinib

8.1.1 Description

Ibrutinib is 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1- piperidinyl]-2-propen-1-one and has a molecular weight of 440.50 g/mole (anhydrous basis). Ibrutinib exhibited 18% to 23% oral bioavailability in rats and 7% to 11% oral bioavailability in dogs. The mean terminal half-life of ibrutinib after oral administration ranged from 1.7 to 3.1 hours in mice, 1 to 4.7 hours in rats, and 3.3 to 6.4 hours in dogs. Preliminary results suggest a 1.5- to 2.5-hour half-life of ibrutinib in humans. The effects of renal and/or hepatic impairment on drug clearance are not known at this time. In vitro studies have indicated that ibrutinib is metabolized extensively by CYP3A4.

8.1.2 Form

Ibrutinib is a white to off-white crystalline solid. Ibrutinib has a single chiral center and is the R-enantiomer. Ibrutinib product is manufactured for Pharmacyclics LLC by a contract manufacturer. Ibrutinib PO Hard Gelatin Capsule is an oral formulation containing micronized ibrutinib and the following compendial excipients: microcrystalline cellulose (NF); croscarmellose sodium (NF); sodium lauryl sulfate (NF); magnesium stearate (NF). The 140 mg strength contains 140 mg of the active ingredient, ibrutinib, adjusted for water content and purity in a size 0, gray, hard gelatin capsule. The 70 mg strength contains 70 mg of the active ingredient, ibrutinib, adjusted for water content and purity in a size 2, yellow, hard gelatin capsule. Capsules are packaged in high-density polyethylene (HDPE) bottles with an induction seal and a child resistant screw top cap. Each bottle is distributed by Pharmacyclics LLC/AbbVie Inc. The number of capsules per bottle is indicated on the label. The HDPE bottles are labeled with the appropriate information and intended for distribution to participants. Empty HDPE bottles will not be supplied by Pharmacyclics LLC/AbbVie Inc.

8.1.3 Storage and Stability

The recommended storage condition for ibrutinib PO Hard Gelatin Capsule is at 15°C to 25°C [59° F to 77° F] with excursions permitted to 30°C (86°F). Under these conditions, the drug product is expected to remain within specifications for at least 36 months. Temperatures lower than 15°C or greater than 30°C must be reported to Pharmacyclics/AbbVie for evaluation of impact on product quality.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

8.1.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

If a drug shipment arrives damaged, or if there are any other drug complaints, a product complaint must be reported. A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

8.1.5 Availability

Ibrutinib will be supplied free-of-charge from Pharmacyclics LLC/AbbVie Inc for this study.

8.1.6 Administration

Ibrutinib should be self-administered daily by the participant or qualified hospital staff and should be taken at approximately the same time each day. Ibrutinib is intended to be administered orally once daily with 8 ounces (approximately 240 mL) of water (avoid grapefruit juice and Seville orange juice products due to CYP450 3A4 inhibition). The capsules should be swallowed intact and participants should not attempt to open capsules or dissolve them in water.

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose. The missed dose will not be made up and must be returned to the site at the next scheduled visit. If the pills are vomited this should be noted on the diary, but a replacement dose should not be taken that day. A study diary will be used to aid with study drug administration compliance for subjects taking drug in a non-hospital setting.

8.1. Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the study drug. Each site will be responsible for maintaining drug accountability records and lot numbers during the study.

8.1.8 Destruction and Return

Unused ibrutinib capsules will be returned by the participant, collected and counted at each study visit and will be returned to pharmacy for destruction. Unused supplies of ibrutinib will be destroyed according to institutional policies.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

9 STUDY CALENDAR

See study calendar below for screening and follow-up assessments.

	Baseline (Screening)	**Days 1 – 28[1, 4]**	**Day 28 (± 3 days)**	**Follow-up Visit (Day 58 ± 7 days)**
Informed Consent	X			
Demographics	X			
Current and complete medical history (including days of symptom onset to study start, alcohol and tobacco history)	X			
Concurrent medications (including supplements)	X	X	X[4]	X[4]
Physical exam including vitals	X	Daily while in hospital	X[4]	X[4]
Clinical status on 8-Point Scale	X	Daily[8]	X[4,8]	X[4,8]
O_2 saturation and documentation of supplemental O_2, and mechanical/cardiopulmonary support (if any)	X	Daily while in hospital	X	As clinically indicated[4]
Arterial blood gas	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated
CBC with differential (including INR at baseline)	X	Every 7 days or more often, if clinically indicated	X	As clinically indicated[4]
Serum Chemistries, BUN, Cr	X	Every 7 days or more often if clinically indicated	X	As clinically indicated[4]
C-reactive protein, ferritin	X	X (Day 3 ± 1 day, Day 10 ± 1 day)		
Corollary Studies per Section 10	X[2]	X[2] (Day 3 ± 1 day and Day 10 ± 1 day)	X[2]	X[2]
EKG	X[5]	X[5]	X[5]	As clinically indicated

CONFIDENTIAL INFORMATION
No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

	Baseline (Screening)	Days 1 – 28[1, 4]	Day 28 (± 3 days)	Follow-up Visit (Day 58 ± 7 days)
SARS-CoV-2 viral testing by RT-PCR by nasopharyngeal swab	X		X[6]	
B-HCG[7]	X			
Radiological Evaluation	X[3]	As clinically indicated	X[3]	As clinically indicated
Survival status	X	X	X[4]	X[4]
Adverse Events Related or Possibly Related to Ibrutinib		X	X[4]	X[4]
Reason for early study discontinuation (if applicable) noted in medical record		X	X	
Ibrutinib or placebo (once daily)		X	X	
Review subject diary (if applicable)		X	X	

B-HCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; CBC = complete blood count; Cr = creatinine; CT = computed tomography; EKG = electrocardiogram; INR = international normalized ratio; NGT = nasogastric tube; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

1. Treatment for subjects may be stopped at the discretion of the treating physician after 14 days if the subject is clinically stable and has been off supplemental oxygen for > 48 hours or treatment may be discontinued for reasons outlined in Section 5.8. In either case, Day 28 procedures (below) should be performed in the event of hospital discharge, applicable procedures for the Treatment Period should continue until Day 28 (either in hospital or via subject diary), and procedures under Day 28 should still be performed on Day 28 (± 3 days), regardless of when the subject stops receiving study drug.
2. Unless subject is unstable or blood draw is not possible. See corollary studies in Section 10 for research blood collection.
3. Chest x-ray and/or CT scan to be used to meet the criteria as determined by the PI. A similar modality of study may be used for follow-up unless medical resources are limited.
4. A tele-health visit with coordinated diary collection and/or return of ibrutinib is permitted prior to Day 28, at Day 28, and at Day 58 if circumstances prevent a clinic visit. Lab draws and other assessments that may be clinically indicated will be performed through outpatient laboratory or radiology services, or other accessible facilities determined by the treating physician or study team unless it is not medically safe.
5. EKG assessments will be performed for all subjects at baseline, and daily thereafter for the first 3 days, on Day 7, and weekly thereafter while subjects are hospitalized and on study drug. Serial EKGs are not needed for subjects on continuous telemetry during the time they are on telemetry. EKGs should also be performed as clinically indicated.
6. Quantitative assessments are preferred, and same nostril as that used at baseline should ideally be used for testing should be used unless medically not possible (i.e., due to NGT tube insertion).
7. Required for female subjects of child bearing potential.
8. Clinical status on an 8-point ordinal scale (Figure 6) should be recorded taking into account limitations on activities and required supportive care (oxygen or ventilation) in hospital and on diary if discharged.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

10 COROLLARY STUDIES

Serial evaluations of inflammatory and chemo-attractant cytokines, IgM and IgG antibody titers to SARS-CoV-2 will be performed as exploratory studies. These studies will help inform if a clinically meaningful biomarker(s) for response can be identified, and to evaluate if ibrutinib as a BTK-inhibitor impacts humoral response to SARS-CoV-2.

Additional information on the collection, handling/processing, disposition, and measurement methods will be provided in the central lab manual/separate document.

Sampling may not be possible for all collection times in those subjects who are medically unstable or inaccessible or if hospital resources preclude collection. An allowance of ± 1 day is permitted for sample collection for Days 3, 10 due to medical reasons. An allowance of ± 3 days is permitted for Day 28, and 58 blood collections in the event of medical reasons or scheduling conflicts.

Cytokine Studies (Study Wide)

A magnetic multiplex enzyme-linked immunosorbent assays will be used for inflammatory and chemo-attractant cytokine assessments that may include but not limited to: GMCSF, IL1B, IL2, IL6, IL7, IL8, IL10, IP10/CXCL10, MCP-1/CCL2, MIP-1A/CCL3, MIP1B/CCL4, INFγ, IL12p40 and TNF-a (as per studies cited in Table 1) will be performed on samples from subjects on supportive care plus placebo or supportive care plus ibrutinib.

Signaling Studies (Study Wide)

NanoString transcriptome analysis for innate and adaptive immune signaling to investigate immune cell types including T and B-cell subtypes and monocytes will be carried out on subject whole blood.

Serology for SARS-CoV-2 IgM and IgG antibody response (Study Wide)

The kinetics of SARS-CoV-2 IgM and IgG antibody response have not been reported. Both IgM and IgG antibody responses were documented in patients with SARS-CoV-1 infection, with positivity noted 1 week after infection and peak IgM titers at 3 weeks, and a sustained IgG antibody response after Week 3 that peaked at Week 12.[36] Serial evaluations of IgM and IgG antibody titers will be performed by a central laboratory. Any remainder sample material not used in the above studies will be banked for future studies of other response biomarkers.

Statistical Plan for Corollary Studies

All efficacy endpoints will be assessed using corollary study data to identify potential predictors of change in the disease course. These analyses are exploratory in nature and no alpha adjustment will be made to address multiplicity. Mean cytokine and antibody titer changes from baseline between the ibrutinib treated and untreated controls will be analyzed using blocking model designs to account for known confounding factors such as age and gender.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Handling of Samples

Collection tubes for corollary studies will be sourced from the Treon Laboratory at the Dana Farber Cancer Institute. For corollary studies supply and replacement contact [redacted] (Treon Laboratory) at [redacted] or call [redacted].

For cytokine, NanoString, and serology studies, study sites will process locally until end of study or as directed by study sponsor. Sites will utilize sample shipping kit and instructions provided by the sponsor to batch ship samples to central laboratory for testing. Please refer to the central laboratory manual for additional information.

11 DATA REPORTING/REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events: List and Reporting Requirements).

11.1 Source Documents and Case Report Completion

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

11.2 Data Quality Assurance

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11.3 Data Safety Monitoring

An independent data monitoring committee (DMC) will review and monitor toxicity and accrual data from the study on an ongoing basis. The safety and interim efficacy of the study will be monitored by the DMC as outlined in a separate DMC charter. An early safety evaluation will occur by the DMC following the enrollment of 3 - 6 subjects with at least 7 days of follow up and will continue in regular frequency approximately every 3 - 4 weeks until all subjects reach Day 28 or prematurely discontinue from study.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

12 STATISTICAL CONSIDERATIONS

12.1 Study Design and Endpoints

A statistical analysis plan (SAP) will be prepared and finalized prior to interim database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. Any deviations in the planned analysis as stated in the protocol will be delineated in the SAP. Any deviations from the SAP will be reported in the clinical study report (CSR).

Subjects will be randomized 1:1 to ibrutinib + supportive care vs. placebo + supportive care, stratified by prescription for remdesivir. As no standard for treatment of COVID-19 in pulmonary distress currently exists and new treatment options are urgently needed, this study will be exploratory in nature.

Primary Endpoint: The primary endpoint will be the proportion of subjects alive and without respiratory failure at Study Day 28.

Secondary endpoints will include:

- Change in the World Health Organization (WHO)-8 point ordinal scale from baseline between the experimental and control arms at Study Day 14 (Figure 6)
- Median reduction in days spent on supplemental oxygen, with time on supplemental oxygen imputed to the maximum number of days on study drug (28) for all points following the death of a subject,
- All-cause mortality at Study Days (7, 14, 21, and 28),
- Proportion of subjects experiencing respiratory failure or death on Study Days (7, 14, 21, and 28)
- Mechanical ventilation-free survival
- Days on mechanical ventilation
- Duration of hospitalization
- Time to discharge
- PaO2:FiO2 and/or oxygenation index, and
- Safety and tolerability of ibrutinib as an adjuvant therapy to standard of care as assessed by treatment emergent adverse events (TEAEs), serious adverse events (SAEs), related AEs, TEAEs by grade, and abnormal laboratory findings. Type, frequency, seriousness and relatedness of TEAEs will be analyzed according to the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory abnormalities will be analyzed according to NCI CTCAE v5.0.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Respiratory failure is defined by clinical diagnosis of respiratory failure and initiation of 1 of the following therapies:

1. Endotracheal intubation and mechanical ventilation,
2. Extracorporeal membrane oxygenation,
3. High-flow nasal cannula oxygen delivery (i.e., reinforced nasal cannula delivering heated, humidified oxygen with fraction of delivered oxygen ≥ 0.5 and flow rates of ≥ 30 L/min),
4. Noninvasive positive pressure ventilation,
5. Clinical diagnosis of respiratory failure with initiation of none of these measures only when clinical decision-making driven is driven solely by resource limitation (these events must be formally collected as data and flagged, for purposes of sensitivity analyses).

These study endpoints are in alignment with other ongoing studies in COVID-19; in particular, many studies use a similar ordinal scale assessment (NCT04292899; NCT04315298) as in the first secondary endpoint.

Figure 6. Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

ECMO = extracorporeal membrane oxygenation; RRT = renal replacement therapy

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

12.2 Sample Size Justification

Forty-six subjects will be randomized at an allocation of 1:1 to supportive care plus placebo or supportive care plus ibrutinib, stratified by prescription for remdesivir. Baseline is assessed at the time of randomization, which based on the acute nature of study subjects is likely to be on the same day as initiation of study drug. The proportion of subjects alive, without respiratory failure at 28 days of control arm is assumed to be 60% and the experimental arm is assumed to 90%. Forty-six subjects total are required to achieve ≥ 80% power with 1-sided alpha = 0.1. Replacement may be implemented for subjects that withdraw consent or are lost to follow up prior to Day 28.

12.3 Interim Analysis

One interim analysis using the gamma family spending function with a conservative boundary (parameter = –4) for futility (non-binding) will be conducted after 18 subjects are randomized and treated/followed for at least 28 days. The DMC will review and evaluate efficacy and safety results while the sponsor remains blinded.

In addition, an analysis to estimate the overall proportion and number of subjects alive and without respiratory failure will be conducted in a blinded fashion when approximately 70% of the planned subjects in the FAS population (i.e., 32 subjects) have completed the Day 28 Visit or died. The objective of this analysis to re-estimate sample size if needed. If the final sample size is increased > 20% from the initial sample size (i.e., final sample size > 56 subjects), then an additional interim analysis may be conducted after 46 subjects have completed the Day 28 visit or discontinued from the study. The Lan-Demets alpha spending function based on O'Brien-Fleming boundary for superiority assessment and the gamma family spending function with a conservative boundary (parameter = –4) for non-binding futility assessment will be utilized at this interim analysis. The DMC will review and evaluate efficacy and safety results while the sponsor remains blinded.

12.4 Efficacy Analysis

All efficacy analyses will be performed using the Full Analysis Set (FAS) which will include all subjects who are randomized and received at least one dose of study drug. Subjects will be grouped according to treatment as randomized. In addition, a supplemental analysis of the primary and secondary efficacy endpoints will be performed for the modified FAS which will include all randomized and dosed subjects who have assessment through Day 28 or die before Day 28. All details of analysis methods will be described in the statistical analysis plan.

The primary analysis will occur after all subjects have completed the Day 28 Visit or prematurely discontinued study. The data for the primary analysis will be locked after data cleaning. Data after the Day 28 Visit will be added to a new version of the database which will be cleaned and locked at the end of the study. The sponsor will be unblinded at the primary analysis.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

12.5 Safety Analysis

Safety data will be generated from the Safety Population which consists of all subjects receiving at least 1 dose of study drug (ibrutinib or placebo). Subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

Detailed tabulations of safety data (AEs, clinical laboratory tests and other safety endpoints) will be summarized by treatment arm for the safety population.

12.6 Sample Size, Accrual Rate and Study Duration

Subjects will be randomized 1:1 in a placebo-controlled, double blinded study to receive either supportive care and placebo **or** supportive care and ibrutinib for up to 28 days. For subjects randomized to receive ibrutinib, the dose of ibrutinib will be 420 mg a day. Approximately 46 subjects will be enrolled in this study. Subjects that withdraw consent or are lost to follow up from the study before Day 28 may be replaced. Enrollment is anticipated to be complete within 3 - 6 months of activation. The study is expected to be complete within 6 - 9 months after activation.

13 ETHICS

13.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

13.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

13.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

14 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last subject's last visit.

15 PUBLICATION PLAN

Time to presentation or publication is expected within 6 - 9 months after study activation. Any formal presentation or publication of data from this trial may be published after review and comment by Pharmacyclics LLC/AbbVie Inc prior to any outside submission. Pharmacyclics LLC/AbbVie Inc must receive copies of any intended communication in advance of publication (3 days for presentational materials, abstracts, manuscripts). These requirements acknowledge Pharmacyclics LLC/AbbVie's responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. The principal investigator shall have the final authority to determine the scope and content of resulting publications, provided such authority shall be exercised with reasonable regard for proprietary interests and not permit disclosure of confidential or proprietary information that belongs to Pharmacyclics LLC/AbbVie Inc.

16 REFERENCES

1. Guan WJ, et al. Clinical characteristics of coronavirus disease 2019 in China. NEJM 2020; Feb 28. doi: 10.1056/NEJMoa2002032.
2. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323:1061-69.
3. Bhatraju PK, et al. Covid-19 in critically ill patients in the Seattle region-case series. NEJM 2020. DOI: 10.1056/NEJMoa2004500.
4. Cao B, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. NEJM 2020.
5. Wu C, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA 2020; Published online March 13, 2020. doi:10.1001/jamainternmed.2020.0994.
6. Hoffman M, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020. Mar 4. pii: S0092-8674(20)30229-4.
7. Fujino N, et al. isolation of alveolar epithelial type II progenitor cells from adult human lungs. Lab Invest. 2010; 91:363-78.
8. Pechkovsky D, et al. CCR2 and CXCR3 chemokines are differentially expressed and regulated in human alveolar epithelial cells type II. Resp. Res. 2005;6:75.
9. Wang J, et al. Differentiated human alveolar type II cells secrete antiviral IL-29 in response to influenza A infection. J Immunology. 2009;182:1296-304.
10. Thorley AJ, et al. Innate immune responses to bacterial ligands in the peripheral human lung-role of alveolar epithelial TLR expression and signaling. PLOS ONE. 2011;6:e21827.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

11. Chuquimia O, et al. Alveolar epithelial cells are critical in protection of the respiratory tract by secretion of factors able to modulate the activity of pulmonary macrophages and directly control bacterial growth. Infection and Immunity. 2013;81:381-89.
12. Werner JL, Steele C. Innate receptors and cellular defense against pulmonary infections. J. Immunology. 193:3842-50.
13. He L, et al. Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARS patients: relation to acute lung injury and pathogenesis of SARS. J. Pathology. 2006;210:288-97.
14. Jiang Y, et al. Characterization of cytokine/chemokine profiles of severe acute respiratory syndrome. Am J Respir Care Med. 2005;171:850-57.
15. Ley K. M1 means Kill; M2 means Heal. J. Immunology. 2017;199:2191-93.
16. Atri C, et al. Role of human macrophage polarization in inflammation during infectious diseases. Int J Mol. Sci. 2018;19:1801.
17. Chan JF, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect. 2020;9:221-36.
18. Heurich A, et al. TMPSSR2 and ADAM17 cleave ACE2 differentially and only proteolysis by TMPSSR2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein. J Virology. 2014;88:1293-307.
19. Huang C, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:565-74.
20. Jeffries CA, et al. Bruton's tyrosine kinase is a Toll/interleukin-1 receptor domain-binding protein that participates in nuclear factor kappaB activation by Toll-like receptor 4. J Biol. Chem. 2003;278:26258-64.
21. Yang G, et al. A mutation in MYD88 (L265P) supports the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase in Waldenström macroglobulinemia. Blood. 2013;122:1222-32.
22. Yang G, et al. HCK is a survival determinant transactivated by mutated MYD88, and a direct target of ibrutinib. Blood. 2016;127:3237-52.
23. Wang Y, Liu L. The Membrane Protein of Severe Acute Respiratory Syndrome Coronavirus Functions as a Novel Cytosolic Pathogen-Associated Molecular Pattern To Promote Beta Interferon Induction via a Toll-Like-Receptor-Related TRAF3-Independent Mechanism. mBio. 2016;7(1):e01872-15. doi: 10.1128/mBio.01872-15.
24. Chen JG, et al. $BTK^{Cys481Ser}$ drives ibrutinib resistance via ERK1/2 and protects $BTK^{wild\text{-}type}$ MYD88-mutated cells by a paracrine mechanism. Blood. 2018;131:2047-59.
25. Ernst M, et al. Constitutive activation of the SRC family kinase HCK results in spontaneous pulmonary inflammation and an enhanced innate immune response. J Exp Med. 2002;196:589-604.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

26. Tian S, et al. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. J Thoracic Oncology. 2020;Feb 28. pii: S1556-0864(20)30132-5.
27. Yao XH, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. Zhonghua Bing Li Xue Za Zhi. 2020 Mar 15;49(0):E009.
28. Available from: https://lincs.hms.harvard.edu/db/datasets/20222/results?page=1
29. Byrd JC, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013;369:32-42.
30. Niemann CU, et al. Disruption of *in vivo* Chronic Lymphocytic Leukemia Tumor–Microenvironment Interactions by Ibrutinib – Findings from an Investigator-Initiated Phase II Study. Clin Cancer Res. 2015;22:1572-82.
31. Vos JM, et al. CXCL13 levels are elevated in patients with Waldenström macroglobulinemia, and are predictive of major response to ibrutinib. Haematologica. 2017;102:e455.
32. Miklos D, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Blood. 2017;130:2243-50.
33. Greil R, et al. Ibrutinib decreases obinutuzumab induced secretion of cytokines associated with infusion related reactions in patients with CLL: Analysis from the ILLUMINATE study. Proc. ICML 2019 (Hematological Oncology 37(2):210-12.
34. Florence JM, et al. Inhibiting Bruton's tyrosine kinase rescues mice from lethal influenza induced acute lung injury. Am J Physiol. Lung Cell Mol. Physiol. 2018;315:L52-58.
35. Treon S, Castillo J, Skarbink A, et al. The BTK-inhibitor ibrutinib may protect against pulmonary injury in COVID-19 infected patients. Blood 2020: e-pub ahead of print 2020/01/17; doi: https://doi.org/10.1182/blood.2020006288.
36. Li G, Chen X, Xu A. Profile of specific antibodies to the SARS-Associated coronavirus. N Engl J Med. 2003;349(5):508-9.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ACE2+	Alveolar Type II
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BTK	Bruton's Tyrosine Kinase
cGVHD	chronic graft versus host disease
CLL	chronic lymphocytic leukemia
COVID-19	Coronavirus disease 2019
CrCl	creatinine clearance
CRP	c-reactive protein
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DMC	Data Monitoring Committee
eCRF	electronic case report form
EDC	electronic data capture
EKG	electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
HCK	hematopoietic cell kinase
HCQ	hydroxychloroquine
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL	interleukin

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

ILD	interstitial lung disease
IMP	Investigational Medicinal Product
IP10/CXCL10	interferon-inducible protein 10
IRB	Institutional Review Board
LPS	lipopolysaccharide
MCL	mantle cell lymphoma
MCP-1	monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NGT	nasogastric tube
PBS	phosphate-buffered saline
PCR	polymerase chain reaction
P-gp	P-glycoprotein
RT	reverse transcriptase
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SLL	small lymphocytic leukemia
SUSAR	suspected unexpected serious adverse reaction
TA MD	Therapeutic Area Medical Director
TLR	Toll-like receptors
TNF-a	tumor necrosis factor alpha
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WM	Waldenström's macroglobulinemia

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M20-310 (PCYC-1150-IM): **i**bruti**N**ib in **S**ARS CoV-2 induced **P**ulmonary **I**njury and **R**espiratory failur**e** (iNSPIRE)

Protocol Date: 06 July 2020

Clinical research studies sponsored by AbbVie are subject to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date
Name of Principal Investigator (printed or typed)	

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

APPENDIX C. INHIBITORS AND INDUCERS OF CYP3A

NOTE: Itraconazole and ketoconazole can be replaced with voriconazole for study subjects.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	carbamaze
indinavir	nevirapine
nelfinavir	barbiturates
ritonavir	glucocorticoids
clarithromycin	modafinil
Itraconazole	oxcarbazepine
Ketoconazole	pioglitazone
nefazodone	troglitazone
saquinavir	pioglitazone
suboxone	**Strong CYP3A inducers**
telithromycin	avasimibe
cobicistat	carbamazepine
boceprevir	phenobarbital
mibefradil	phenytoin
telaprevir	rifabutine
troleandomycin	rifampin
posaconazole	St. John's Wort
voriconazole	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
isavuconazole	
crizotinib	
darunavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
imatinib	
Weak inhibitors:	
cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delavirdine	
gestodene	
mifepristone	
norfloxacin	
star fruit	

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

APPENDIX D. GUIDANCE ON POSSIBLE DRUG INTERACTIONS FOR IBRUTINIB AND MEDICATIONS THAT MAY BE IN USE TO TREAT COVID-19

Drug	Drug-Drug Interaction Potential with Ibrutinib	Ibrutinib Dosing Recommendation
Azithromycin	No clinically relevant effect on CYP3A	No dose adjustment
Favipiravir	Low DDI potential	No dose adjustment
Hydroxychloroquine	No clinically relevant effect on CYP3A	No dose adjustment
Lopinavir + ritonavir	Strong CYP3A inhibitor	Reduce ibrutinib to 140 mg
Remdesivir	In vitro CYP3A inhibitor. Low potential for clinically relevant CYP3A effect.	No dose adjustment

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

APPENDIX E. CHILD-PUGH SCORE FOR SUBJECTS WITH LIVER IMPAIRMENT

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	< 34 (< 2)	34 - 50 (2 - 3)	> 50 (> 3)
Serum albumin, g/L (g/dL)	> 35 (> 3.5)	28 - 35 (2.8 - 3.5)	< 28 (< 2.8)
PT/INR	< 1.7	1.71 - 2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I - II (or suppressed with medication)	Grade III - IV (or refractory)

INR = international normalized ratio; PT = prothrombin time

Points	Class
5 - 6	A
7 - 9	B
10 - 15	C

Source:

1. Child CG, Turcotte JG. Surgery and portal hypertension. In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964;50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, et al. Transection of the oesophagus for bleeding oesophageal varices. The British journal of surgery. 1973;60:646-9.

CONFIDENTIAL INFORMATION
No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

APPENDIX F. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 2.0	03 May 2020
Version 1.0	22 April 2020

The purpose of this Version is to make the following updates:

- Increased number of potential study sites

  Rationale: To ensure that the study can be fully enrolled in a timely manner.

- Revised eligibility criteria to allow subjects to be on oxygen therapy for up to 5 days, removed the 6 L limit on oxygen therapy, and clarified restrictions on concurrent malignancy.

  Rationale: To reduce burden around timing of enrollment to allow more subjects access to therapy.

- Removed recommendation for subjects to avoid corticosteroid use.

  Rationale: Based on recent publications and updates to standard of care for the treatment of COVID-19.

- Adjusted resolution criteria for bleeding events

  Rationale: Many low-grade bleeding events (e.g., petechiae, echymoses) are not expected to completely resolve immediately and pose little risk to subjects.

- Revisions to ibrutinib stability description.

  Rationale: Correction of error.

- Updated details regarding the planned and potential interim analyses.

  Rationale: To allow for a potential additional interim analysis to be conducted in case of a relatively large increase in the final sample size. A group sequential design is specified to provide strong control of the type 1 error rate at this potential analysis.

- Updated drug interaction guidance for compounds that may be used to treat COVID-19.

  Rationale: To align with evolving treatment standards for COVID-19.

- Made minor clarifications to the study calendar.

  ***Rationale*:** To address questions from study sites.

In addition, minor clerical errors were corrected and edits for consistency within the document were made.

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.