BMT 29

A Pilot Study of INCB039110 (Itacitinib) for the Treatment of Steroid Refractory Chronic Graft-Versus-Host Disease

SARAH CANNON DEVELOPMENT INNOVATIONS STUDY NUMBER:	BMT 29
STUDY DRUG:	INCB39110 (Itacitinib)
SPONSOR:	Sarah Cannon Development Innovations, LLC (Innovations) 1100 Dr. Martin L. King Jr. Blvd. Suite 800 Nashville, TN 37203 1-844-710-6157 asksarah@sarahcannon.com
STUDY CHAIR:	Carlos Bachier, MD Program Director, Blood and Marrow Transplant Sarah Cannon Center for Blood Cancer 2410 Patterson Street, Suite 500 Nashville, TN 37203 615-342-4914 Office 210-364-3897 Cell
DATE FINAL:	11 July 2019

AMENDMENT NUMBER:	**1**	**AMENDMENT DATE:**	**20 August 2019**
AMENDMENT NUMBER:	**2**	**AMENDMENT DATE:**	**13 December 2019**
AMENDMENT NUMBER:	**3**	**AMENDMENT DATE:**	**08 June 2021**
AMENDMENT NUMBER:	**4**	**AMENDMENT DATE:**	**26 October 2021**

SARAH CANNON
Fighting Cancer Together™

Clinical Study Statement of Compliance

A Pilot Study of INCB039110 (Itacitinib) for the Treatment of Steroid Refractory Chronic Graft-Versus-Host Disease

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

SARAH CANNON
Fighting Cancer Together™

Clinical Study Protocol Approval Page

A Pilot Study of INCB039110 (Itacitinib) for the Treatment of Steroid Refractory Chronic Graft-Versus-Host Disease

INNOVATIONS STUDY NUMBER:	BMT 29
STUDY DRUG:	INCB39110 (Itacitinib)
DATE FINAL:	11 July 2019

AMENDMENT NUMBER:	**1**	**AMENDMENT DATE:**	**20 August 2019**
AMENDMENT NUMBER:	**2**	**AMENDMENT DATE:**	**13 December 2019**
AMENDMENT NUMBER:	**3**	**AMENDMENT DATE:**	**08 June 2021**
AMENDMENT NUMBER:	**4**	**AMENDMENT DATE:**	**26 October 2021**

Carlos Bachier, MD

Study Chair
Program Director, Blood and Marrow Transplant
Sarah Cannon Center for Blood Cancer
2410 Patterson Street, Suite 500
Nashville, TN 37203

Study Chair Signature

Date

Marcy Vallone

Vice President
Sarah Cannon Development Innovations, LLC
1100 Dr. Martin L. King Jr. Blvd.
Suite 800
Nashville, TN 37203

Sarah Cannon Development Innovations, LLC Representative Signature

Date

SARAH CANNON
Fighting Cancer Together™

Clinical Study Principal Investigator Signature Form

A Pilot Study of INCB039110 (Itacitinib) for the Treatment of Steroid Refractory Chronic Graft-Versus-Host Disease

INNOVATIONS STUDY NUMBER:	BMT 29		
DATE FINAL:	11 July 2019		
AMENDMENT NUMBER:	**1**	**AMENDMENT DATE:**	**20 August 2019**
AMENDMENT NUMBER:	**2**	**AMENDMENT DATE:**	**13 December 2019**
AMENDMENT NUMBER:	**3**	**AMENDMENT DATE:**	**08 June 2021**
AMENDMENT NUMBER:	**4**	**AMENDMENT DATE:**	**26 October 2021**

By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

_____	_____	_____
Principal Investigator Name (Please Print)	**Principal Investigator Signature**	**Date**

Please retain a copy of this page for your study files and return the original signed and dated form to:

Sarah Cannon Development Innovations, LLC
1100 Dr. Martin L. King Jr. Blvd., Suite 800
Attention: BMT 29 Study Team
Nashville, TN 37203

CLINICAL PROTOCOL AMENDMENT SUMMARY OF CHANGES
BMT 29

AMENDMENT NUMBER: 1	AMENDMENT DATE: 20 August 2019

Additions to the text are **bolded** and deletions from the text are ~~crossed-off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Section 3.1 Inclusion Criteria

Corrected Inclusion Criterion #9 to state that the hematologic function requirements are in Inclusion Criterion #5.

9. Adequate hematologic function as defined in Inclusion Criterion #~~3~~**5**.

Table 2 Guidelines for Interruption and Restarting of Itacitinib

Altered the proposed dose modifications for bilirubin elevations for patients for whom the bilirubin is increasing in the presence of GVHD response and cannot be attributed to GVHD or concomitant therapy. The new requirement is that the medication should be **held or dose reduced immediately and restarted or re-escalated if the repeat value obtained 7 days later shows no persistent elevation.**

Table 2 Guidelines for Interruption and Restarting of Itacitinib

Adverse Event	Action Taken
Chemistry	
Total bilirubin elevations that occur in the presence of GVHD response that cannot be attributed to new liver GVHD or concomitant therapy.	Total bilirubin is 3.0 to 5.0 x ULN: • **Repeat** assessment within 7 days. If elevation persists: – **Immediately hold or r~~R~~educe** dose by 1 level until bilirubin ≤1.5 x ULN – **Re-escalate or ~~R~~r**esume previous dose if **the repeat value obtained 7 days later shows no persistent elevation.** ~~resolved in 14 days; if >14 days, maintain reduced dose.~~ Total bilirubin is >5.0 to 10.0 x ULN: • **Repeat** assessment within 7 days. If elevation persists: – **Immediately ~~I~~i**nterrupt until bilirubin is ≤1.5 x ULN. – **Monitor** liver function tests weekly or more frequently as appropriate. – **Re-escalate or ~~R~~r**esume previous dose if **the repeat**

Table 2 Guidelines for Interruption and Restarting of Itacitinib

Adverse Event	Action Taken
	value obtained 7 days later shows no persistent elevation.~~resolved in 14 days; if >14 days, resume at reduced dose.~~ Total bilirubin is >10.0 x ULN: • **Repeat** assessment within 7 days. If elevation persists: – **Interrupt** until bilirubin is ≤1.5 x ULN. – **Re-escalate or ~~R~~r**esume at reduced dose if **the repeat value obtained 7 days later shows no persistent elevation.**~~resolved in 14 days~~; if >**7**~~14~~ days, discontinue treatment and monitor as appropriate.

Additions to the text are **bolded** and deletions from the text are ~~crossed-off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Section 3.2 Exclusion Criteria

Exclusion criteria #2 was revised to exclude patients on JAK therapy for chronic GVHD, but permit prior JAK therapy for acute GVHD.

2. ~~Prior treatment with a~~**Receiving concomitant** JAK inhibitor for **c**GVHD**; prior treatment with a JAK inhibitor for aGVHD is permitted**

Section 5.1.1 Primary Efficacy Period (Cycle 1 Through End of Cycle 6)

Updated study drug dispension schedule to Day 1 for all cycles.

The primary efficacy period is defined as Cycle 1 through the end of Cycle 6. A cycle is 28 days. Study treatment will begin on Cycle 1 Day 1 and study drug will be dispensed **on Day 1 of each cycle.**~~per the following schedule:~~

- ~~Cycle 1: Days 1, 8, 15, and 22~~
- ~~Cycles 2 to 6: Day 1 of each cycle (±7 days)~~

Section 6.3.1 Day 1 of Each Cycle

Updated study drug dispension schedule to Day 1 for all cycles.

- ~~Dispense study drug & Dosing Diary Cycle 1 and d~~Dispense **study drug**, collect **unused drug from previous cycle**, and check compliance~~ on Day 1 of all other cycles~~.

Section 6.7.12 Study Drug Diary and Appendix D: BMT 29 Schedule of Assessments

Removed requirement for patient diaries.

~~6.7.12 Study Drug Diary~~

~~Patients will be given a study drug diary to record the details of each dose of study drug. Diaries will be dispensed/collected on Day 1 of each cycle. Compliance with oral dosing will be confirmed by counting returned tablets and cross-checking with the dosing diaries, which will be examined at these visits.~~

Dispense/Collect Study Drug ~~& Dosing Diary~~

Additions to the text are **bolded** and deletions from the text are ~~crossed-off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Section 3.1 Inclusion Criteria

Inclusion criterion #2 was revised to the following:

2. Male and female patients 18 years-of-age or older who have undergone ~~one~~ allo-HSCT**(s)** from any donor HLA type (related or unrelated donor with any degree of HLA matching) using any graft source (bone marrow, peripheral blood stem cells, or cord blood). Recipients of non-myeloablative, myeloablative, and reduced intensity conditioning are eligible.

Section 3.2 Exclusion Criteria

Exclusion criterion #1 was deleted.

~~1. Has received >1 prior allo-HCT or donor lymphocyte infusion (DLI)~~

Sections 5, 5.3 Treatment Duration, Synopsis, and Study Assessment Table Footnote a

While patients are expected to receive study treatment for approximately 1 year, **patients seeing clinical benefit may stay on treatment for an additional year**.

Patients will be followed for survival for 1 year after the last dose of study drug. The total duration of the study is planned to be **at least**~~approximately~~ 3½ years.

Section 5.4.2 Restricted Concomitant Medications

The following medications have restrictions on use during the treatment period of the study:

• Medications that interfere with coagulation or platelet function including, but not limited to, aspirin in doses exceeding 81 mg/day and related drugs such as heparin and warfarin sodium (Coumadin®) are not permitted. Low-dose aspirin (≤81 mg per day) is permitted, unless clinically contraindicated, as is the use of low molecular weight heparin. If concomitant administration of an anticoagulant/antiplatelet medication is indicated, then caution and enhanced monitoring is required; **it is suggested that CBCs be checked every 1 to 2 weeks for the first 2 cycles of administration.** History of thrombocytopenia should be a factor in the choice of anticoagulant and dose.

Section 6.3 Study Assessment Timing and Study Assessment Table Footnotes

Clarification was added in each subsection that all lipid panel tests will be done in the **fasted** state.

Section 6.7.7 Laboratory Assessments

Laboratory samples (hematology, lipids **[fasting]**, clinical chemistry, urinalysis, and virology [screening and as clinically indicated]) are to be collected as outlined in Appendix D. Safety

laboratory analyses will be performed. Laboratory results will be graded using NCI CTCAE Version 5.

~~Details are presented in the Laboratory Manual.~~

Section 7.1 Itacitinib

Itacitinib will be administered orally at a starting dose of 200 mg once QD (2 x 100 mg tablets), and may be taken **with or** without food.

Section 7.1.3 Instructions for Patients for Handling Itacitinib

Patients must be instructed on the handling of itacitinib as follows:

- ~~To refrain from taking study medication on the d~~**On d**ays of clinic visits, **tablets can to taken before the visit or at the clinic** ~~until~~ after blood samples are collected.

Additions to the text are **bolded** and deletions from the text are ~~crossed-off~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Section 3.2 Exclusion Criteria

Exclusion Criterion #1 was revised to the following:

1. Receiving concomitant JAK inhibitor for chronic GVHD; prior treatment with a JAK inhibitor for acute GVHD is permitted **if treatment was stopped more than 60 days prior to study start. Patients are eligible if JAK inhibitors for treatment of cGVHD are stopped due to side effects and not due to refractoriness**.

BMT 29 PROTOCOL SYNOPSIS

Title of Study:	A Pilot Study of INCB039110 (Itacitinib) for the Treatment of Steroid Refractory Chronic Graft-Versus-Host Disease	
Innovations Study Number:	BMT 29	
Sponsor:	Sarah Cannon Development Innovations, LLC	
Study Duration:	The total duration of the study is planned to be at least 3½ years.	**Phase of Study:** II
Study Centers:	This study will be conducted at approximately 10 sites in the United States.	
Number of Patients:	Up to 40 patients are planned to be enrolled in this study.	
Objectives:	**Primary Objective** The primary objective of this study is to determine: • The overall GVHD response rate defined as the proportion of patients demonstrating a complete response or partial response after 6 months of treatment with itacitinib as defined by National Institute of Health Consensus Criteria (Lee et al. 2015) in patients with steroid-refractory chronic graft-versus-host disease. **Secondary Objectives** The secondary objectives of this study are to determine the: • Ability to either withdraw or decrease steroids to <0.5 mg/kg of methylprednisolone or equivalent • Overall survival • Safety and tolerability of itacitinib in patients with steroid-refractory chronic graft-versus-host disease. • Quality of life impact using the Lee Symptom Scale from screening until the end-of-treatment visit. • Recurrence or progression of chronic GVHD (cGVHD) • Relapse rate of underlying malignancy.	
Study Design:	This is an open-label, multi-center, single-arm pilot study in patients who have been receiving immunosuppressive therapy for the treatment of cGVHD for a duration of >6 months prior to starting daily itacitinib treatment in this study. While patient participation is expected to be approximately 12 months, patients seeing clinical benefit may stay on treatment for an additional year. Patients will continue to receive their systemic immunosuppressive regimen of corticosteroids for steroid-refractory chronic graft-versus-host disease per standard of care by the Investigator during the screening and treatment periods. In addition, transfusion support, continued use of anti-infective medications, and topical steroid therapy is permitted. Chronic GVHD staging and grading will be assessed for efficacy as per NIH Consensus Criteria (Jagasia et al. 2015). Safety and tolerability will be assessed as per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.	
Study Drug, Dose, and Mode of Administration:	Itacitinib 200 mg will be administered orally once daily for up to 24 months. For patients with no GVHD response/stable GVHD after 2 months of therapy at 200 mg a day, the dose will increase to 300 mg once daily. If a patient has achieved a complete GVHD response or partial GVHD response after 6 months of treatment, Investigators may begin to taper the dose of itacitinib by 1 dose level provided corticosteroids have been discontinued for at least 8 weeks following institutional guidelines.	

Main Inclusion Criteria:	1. Eligible male and female patients 18 years-of-age or older who have undergone allogeneic hematopoietic stem cell transplant(s) from any donor HLA type (related or unrelated donor with any degree of HLA matching) using any graft source (bone marrow, peripheral blood stem cells, or cord blood). Recipients of non-myeloablative, myeloablative, and reduced intensity conditioning are eligible. 2. Active, clinically diagnosed, moderate or severe cGVHD per NIH Consensus (Jagasia et al. 2015; Appendix G) a) Moderate cGVHD: At least 1 organ (except lung) with a score of 2, ≥3 organs involved with a score of 1, or lung score of 1. b) Severe cGVHD: At least 1 organ with a score of 3, or lung score of 2 or 3 3. cGVHD must be refractory to steroids defined by at least one of the criteria below: a) Patient is refractory to glucocorticoid therapy at screening, defined as ongoing treatment with prednisone or equivalent ≥0.20 mg/kg/day x 4 weeks at screening and organ progression documented 4 weeks after the initiation of this regimen. b) Patient is dependent on glucocorticoid therapy at screening, defined as treatment with a prednisone equivalent mean dose ≥0.20 mg/kg/day received for 12 weeks at screening. c) Patient is intolerant to glucocorticoids at screening, defined as ongoing treatment with prednisone equivalent ≥0.20 mg/kg/day x 4 weeks at screening and presence of at least one documented glucocorticoid toxicity. 4. Evidence of myeloid and platelet engraftment (absolute neutrophil count [ANC] >1,000/mm^3 AND platelet count >25,000/mm^3). Use of growth factors or platelet transfusions is not allowed within 7 days before screening laboratory assessment. 5. Patients must currently be receiving systemic corticosteroids or other immunosuppressive therapies for the treatment of cGVHD for a duration of >6 months prior to start of study treatment. 6. Patients must be able to swallow and retain oral medication. 7. Patients with an Eastern Cooperative Oncology Group performance status of 0, 1, or 2.
Main Exclusion Criteria:	1. Receiving concomitant JAK inhibitor for chronic GVHD; prior treatment with a JAK inhibitor for acute GVHD is permitted if treatment was stopped more than 60 days prior to study start. Patients are eligible if JAK inhibitors for treatment of cGVHD are stopped due to side effects and not due to refractoriness. 2. Treatment with any other investigational agent, device, or procedure, within 28 days (or 5 half-lives, whichever is longer) of enrollment. For previous study drugs where 5 half-lives is <28 days, a minimum of 10 days between termination of that study drug and administration of itacitinib is required. 3. Pregnant or nursing (lactating) women 4. Patients with relapsed primary malignancy, or who have been treated for relapse after the allogeneic hematopoietic stem cell transplant was performed 5. History of progressive multifocal leuko-encephalopathy.
Statistical Methodology:	No formal hypothesis testing is planned for this exploratory study. In order to estimate the overall response rate in this population, a 95% exact two-sided confidence interval will be calculated. A sample size of 40 produces a two-sided 95% CI with a width equal to 0.266 when the sample proportion is 0.200.

BMT 29 CONTACT INFORMATION

Sarah Cannon Development Innovations Contact Information:	Sarah Cannon Development Innovations 1100 Dr. Martin L. King Jr. Blvd. Suite 800 Nashville, TN 37203 1-844-710-6157 asksarah@sarahcannon.com
Study Chair:	Carlos Bachier, MD Program Director, Blood and Marrow Transplant Sarah Cannon Center for Blood Cancer 2410 Patterson Street, Suite 500 Nashville, TN 37203 615-342-4914 Office 210-364-3897 Cell Carlos.Bachier@hcahealthcare.com
Safety Dept. Fax #: **Safety Dept. Email:**	1-866-807-4325 CANN.SAE@scri-innovations.com
Medical Support Center Phone # **Regulatory Department Email:**	1-844-710-6157 SCRIRegulatory@SCRI-Innovations.com
Innovations Enrollment Fax #: **Innovations Enrollment Email #:**	1-866-346-1062 or 615-524-4012 CANN.SCRIInnovationsEnr@scri-innovations.com

LIST OF ABBREVIATIONS

AE	Adverse event
Allo-HSCT	Allogeneic hematopoietic stem cell transplant
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
CFR	Code of Federal Regulations
CI	Confidence interval
CR	Complete response/remission
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GVHD	Graft-versus-host disease (a [acute], c [chronic])
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
Innovations	Sarah Cannon Development Innovations
IRB	Institutional Review Board
JAK	Janus kinase
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIH	National Institute of Health
NR	No response
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PHI	Protected health information
PR	Partial response/remission
QD	*Quaque die* (each day)
SAE	Serious adverse event
SAR	Suspected adverse reaction
SD	Stable disease
SR-cGVHD	Steroid-refractory chronic graft-versus-host disease
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of normal

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

1. INTRODUCTION

1.1 Background and Study Rationale

During the last 2 decades, the number of patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) has more than doubled worldwide. Graft-versus-host disease (GVHD) remains the major hurdle to improve allo-HSCT outcome. High mortality rates are seen for patients suffering from steroid-refractory (SR) acute GVHD (aGVHD), while chronic GVHD (cGVHD) is associated with a decreased quality of life (Zeiser et al. 2015).

Depending on a number of patient- and transplant-related variables, the incidence of aGVHD ranges from 10% to 80% with symptoms usually developing 2 to 3 weeks post-transplant. It is estimated that cGVHD affects 30% to 70% of allo-HSCT recipients surviving beyond 100 days, with a median onset of 4 to 6 months following HSCT. Although cGVHD is associated with reduced relapse rates in patients transplanted for leukemia, cGVHD remains the leading cause of late death in HSCT survivors (Garnett et al. 2013).

Management of GVHD is challenging. Immunosuppression with corticosteroids forms the basis of first-line therapy in both aGVHD and cGVHD, but sustained responses are usually seen in <50% of patients and there remains no standard 2nd- and 3rd-line treatment for SR-cGVHD. While evaluation of further therapeutic options is complicated, alternative systematic therapy strategies and the identification of novel therapeutic targets are needed to improve outcomes.

A retrospective survey of 95 patients treated for SR-aGVHD and SR-cGVHD with a Janus kinase (JAK) 1/2 inhibitor, ruxolitinib, in 19 European and US transplant centers highlighted the therapeutic potential of JAK-inhibitors in the treatment of SR-GVHD. Treatment with ruxolitinib was considered safe and well tolerated in the heavily pre-treated patient population. An overall response rate (ORR) above 80% was reported for both SR-aGVHD and SR-cGVHD with median time to response being rapid (<2 weeks). Additional follow-up for patients with SR-aGVHD and SR-cGVHD reported 1-year ORRs of 62.4% and 92.7%, respectively (Zeiser et al. 2015).

A novel, potent, and selective inhibitor of the JAK family of protein tyrosine kinases (TYKs) with selectivity for JAK1, itacitinib (INCB039110 adipate), is the investigational product in this study. Itacitinib is being developed by Incyte Corporation for the treatment of GVHD, solid tumors, B-cell malignancies, myeloproliferative neoplasms, and inflammatory diseases.

1.1.1 Inhibition of JAKs as a Target for Graft-Versus-Host Disease

Pharmacologic inhibition of JAK and signal transducer and activator of transcription (STAT) signaling is anticipated to be a promising therapeutic approach for GVHD. This will achieve the beneficial antileukemia effect and overcome human leukocyte antigen barriers in allo-HSCT (Choi et al. 2012, Choi et al. 2014).

In vivo JAK/STAT-signaling inhibition improved survival of mice developing aGVHD and reduced histopathological GVHD grading, serum levels of pro-inflammatory cytokines, and expansion of allo-reactive luc-transgenic T cells (Spoerl et al. 2014). Ruxolitinib impaired differentiation of CD4+ T cells into IFN-γ and IL-17A–producing cells, both being T-cell

phenotypes linked to GVHD. Additionally, ruxolitinib treatment in allo-HSCT recipients increased FoxP3+ regulatory T cells, which are linked to immunologic tolerance. Itacitinib showed similar pharmacologic inhibition of interferon signaling, resulting in the decreased expression of CXCR3, reduced GVHD, and improved survival when administered for 30 days after allo-HSCT in mice.

Promising preliminary clinical efficacy results with 200 or 300 mg itacitinib monotherapy once each daily (QD) are presented in Section 1.1.2.

1.1.2 Itacitinib in Subjects with Acute Graft-Versus-Host Disease

Itacitinib is currently being studied in several indications including in patients with aGVHD. This pilot study will be the first in patients with SR-cGVHD.

The Itacitinib Investigator's Brochure Version 11 presents preliminary data from Study INCB 39110-108 in which 29 patients with aGVHD had received itacitinib (as of the cut-off date of 13 December 2018) in combination with corticosteroids (prednisone or methylprednisolone). The most frequently reported treatment-emergent adverse events (TEAEs) (≥30%) were consistent with expectations for patients with aGVHD and included peripheral edema (44.8%), diarrhea and thrombocytopenia/platelet count decreased (48.3% each), hyperglycemia (34.5%), anemia, abdominal pain and hypokalemia (37.9% each) and fatigue (31.0%). The most frequently reported treatment-related SAEs was sepsis (6 patients; 20.7%). Other serious TEAEs included acute kidney injury, diarrhea, gastrointestinal hemorrhage, multiple organ dysfunction syndrome and respiratory failure (3 patients each, 10.3%), and abdominal pain, staphylococcal infection and thrombocytopenia (2 patients each; 6.9%). Nine patients (31.0%) had fatal TEAEs. Preliminary pharmacokinetic (PK) analyses indicated that exposures appeared similar in patients with aGVHD, healthy volunteers, and subjects with plaque psoriasis, rheumatoid arthritis, and solid tumors.

Preliminary efficacy results showed ORRs (defined as a complete responses [CRs], very good partial responses, and partial responses [PRs]) at Day 28 of 83.3% for first-line aGVHD subjects treated with 200 or 300 mg itacitinib once QD, and 62.5% and 66.7% were reported at Day 28 for subjects with SR-aGVHD treated with 200 or 300 mg itacitinib once QD, respectively (Itacitinib Investigator's Brochure).

1.2 Potential Risks and Benefits of the Treatment Regimen

Adverse events (AEs) that have been most frequently reported in at least 10% of all subjects receiving itacitinib monotherapy include constipation, anemia, thrombocytopenia, diarrhea, nausea, fatigue, and upper respiratory tract infection.

As a result of itacitinib-mediated immunomodulation, an increased incidence of infections could possibly occur with itacitinib therapy. Strict clinical monitoring is indicated to identify and treat infections in study subjects should they occur.

Because of the potential for myelosuppression, patients will have hematologic parameters closely monitored during clinical studies. If there are clinically relevant declines in hematology parameters, therapy may be interrupted until resolution or discontinuation. Since itacitinib also has the potential to cause white blood cell (WBC) margination (i.e., a transient decrease in

absolute neutrophil count [ANC]), assessment of hematology parameters should be performed before study drug administration and at all applicable study visits.

As described previously, murine models of JAK/STAT inhibition using both ruxolitinib and itacitinib have demonstrated a decrease in the expression of CXCR3, reduction of GVHD, preservation of the beneficial graft-versus-tumor effect, and improvement in survival. To the extent that the thrombocytopenia and anemia observed with ruxolitinib are due to the inhibition of JAK2-mediated erythropoiesis and thrombopoiesis, a selective JAK1 inhibitor would likely be associated with a lower incidence of thrombocytopenia and anemia, while still resulting in a significant reduction in the production and the signaling of inflammatory and immune cytokines. It is therefore of interest to evaluate a selective JAK1 inhibitor in this setting given the hematologic complications associated with GVHD.

In INCB 39110-108, treatment interruptions and stepwise 100 mg dose reductions were used to manage toxicity. In an analysis of the data, efficacy was not affected in patients who demonstrated a Day 28 response and had a dose reduction for any reason. Dose reductions also facilitated platelet recovery in patients receiving treatment. Interestingly, platelet recovery was also observed in patients who did not have a dose reduction. Thus, the proposed itacitinib tapering schedule (see Section 8.3) is not expected to negatively impact efficacy in responding patients, and clinicians are permitted to re-escalate the dose of itacitinib in patients who initiate a taper but subsequently begin to demonstrate signs or symptoms of GVHD progression.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to determine the ORR defined as the proportion of patients demonstrating a cGVHD response of CR or PR after 6 months of treatment with itacitinib as defined by National Institute of Health (NIH) Consensus Criteria (Lee et al. 2015) in patients with SR-cGVHD.

2.2 Secondary Objectives

The secondary objectives of this study are to determine the:

- Ability to either withdraw or decrease steroids to <0.5 mg/kg of methylprednisolone or equivalent
- Overall survival
- Safety and tolerability of itacitinib in patients with SR-cGVHD
- Quality of life impact using the Lee Symptom Scale from screening until the end-of-treatment (EOT) visit
- Recurrence or progression of cGVHD and
- Relapse rate of underlying malignancy.

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria

Patients must meet the following criteria in order to be included in this research study:

1. Written informed consent, according to local guidelines, signed by the patient or by a legal guardian prior to the performance of any study-related screening procedures.
2. Male and female patients 18 years-of-age or older who have undergone allo-HSCT(s) from any donor HLA type (related or unrelated donor with any degree of HLA matching) using any graft source (bone marrow, peripheral blood stem cells, or cord blood). Recipients of non-myeloablative, myeloablative, and reduced intensity conditioning are eligible.
3. Active, clinically diagnosed, moderate or severe cGVHD per NIH Consensus Criteria (Jagasia et al. 2015), Appendix G):
    a) Moderate cGVHD: At least 1 organ (except lung) with a score of 2, ≥3 organs involved with a score of 1 in each organ, or lung score of 1.
    b) Severe cGVHD: At least 1 organ with a score of 3, or lung score of 2 or 3.
4. cGVHD must be refractory to steroids defined by at least one of the criteria below:

    a) Patient is refractory to glucocorticoid therapy at screening, defined as ongoing treatment with prednisone equivalent ≥0.20 mg/kg/day x 4 weeks at screening and organ progression documented 4 weeks after the initiation of this regimen.

    b) Patient is dependent on glucocorticoid therapy at screening, defined as treatment with a prednisone equivalent mean dose ≥0.20 mg/kg/day received for 12 weeks at screening.

    c) Patient is intolerant to glucocorticoids at screening, defined as ongoing treatment with prednisone equivalent ≥0.20 mg/kg/day x 4 weeks at screening and presence of at least one documented glucocorticoid toxicity.
5. Evidence of myeloid and platelet engraftment (absolute neutrophil count [ANC] >1,000/mm^3 AND platelet count >25,000/mm^3. Use of growth factors or platelet transfusions is not allowed within 7 days before screening laboratory assessment.
6. Patients must currently be receiving systemic or other immunosuppressive therapies for the treatment of cGVHD for a duration of >6 months prior to start of study treatment.
7. Patients must be able to swallow and retain oral medication.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1, or 2 (Appendix A).
9. Adequate hematologic function as defined in Inclusion Criterion #5.
10. Adequate renal function defined as creatinine clearance ≥30 mL/min measured or calculated by Cockcroft-Gault equation.

11. Patients willing to avoid pregnancy or father children based on 1 of the following criteria:
    - Women of non-childbearing potential (i.e., surgically sterile by hysterectomy and/or bilateral oophorectomy OR ≥12 months of amenorrhea)
    - Women of childbearing potential who have a negative serum pregnancy test at screening and who agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through the safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix C) should be communicated to the patient and their understanding confirmed.
    - Men who agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through the safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix C) should be communicated to the patient and their understanding confirmed. Male patients must also refrain from donating sperm during their participation in the study and for at least 3 months after completing the study.
12. Ability to understand the nature of this study and to comply with study and follow-up procedures.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Receiving concomitant JAK inhibitor for cGVHD; prior treatment with a JAK inhibitor for aGVHD is permitted if treatment was stopped more than 60 days prior to study start. Patients are eligible if JAK inhibitors for treatment of cGVHD are stopped due to side effects and not due to refractoriness.
2. Treatment with any other investigational agent, device, or procedure, within 28 days (or 5 half-lives, whichever is longer) of enrollment. For previous study drugs where 5 half-lives is ≤28 days, a minimum of 10 days between termination of that study drug and administration of itacitinib is required.
3. Presence of current secondary malignancies with the exception of previously treated in situ carcinoma (i.e., noninvasive), cervical carcinoma Stage 1B or less, and noninvasive basal cell or squamous cell skin carcinoma.
4. Pregnant or nursing (lactating) women
5. Patients with relapsed primary malignancy, or who have been treated for relapse after the allo-HSCT was performed
6. History of progressive multifocal leukoencephalopathy
7. Evidence of the following infections:
    - Active uncontrolled bacterial, fungal, parasitic, or viral infection. Infections are considered controlled if appropriate therapy has been instituted and, at the time of screening, no signs of infection progression are present. Progression of infection

is defined as hemodynamic instability attributable to sepsis, new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without other signs or symptoms will not be interpreted as progressing infection.

- Known human immunodeficiency virus (HIV) infection
- Active tuberculosis infection that developed after allo-HSCT
- Active viral infection confirmed by polymerase chain reaction (PCR) for the BK virus (a polyoma virus), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpes virus 6 (HHV-6).
- Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection that requires treatment, or at risk for HBV reactivation (i.e., positive HBsAg).

8. Severe organ dysfunction unrelated to underlying GVHD, including:
    - Cholestatic disorders or unresolved veno-occlusive disease of the liver (defined as persistent bilirubin abnormalities not attributable to GVHD and ongoing organ dysfunction)
    - Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral itacitinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
    - Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months of enrollment, New York Heart Association Class III or IV congestive heart failure (Appendix B), circulatory collapse requiring vasopressor or inotropic support, or arrhythmia that requires therapy
    - Significant respiratory disease that requires mechanical ventilation support or a resting O_2 saturation <90% by pulse oximetry or FEV1 <30%.
9. Patients requiring platelet transfusions to maintain a platelet count >25,000/mm^3
10. Any corticosteroid therapy for indications other than cGVHD at doses >1 mg/kg/day methylprednisolone or equivalent within 7 days of study start
11. Patients receiving treatment with medications that interfere with coagulation or platelet function including, but not limited to, aspirin dose exceeding 81 mg/day and related drugs such as heparin or warfarin sodium (Coumadin®). Use of low molecular weight heparin is allowed.
12. Known allergies, hypersensitivity, or intolerance to itacitinib or any of its excipients
13. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

3.3 Discontinuation from Study Treatment

Patients will be discontinued from study treatment for any of the following reasons:

- Relapse of underlying malignancy
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- The patient is unable to tolerate itacitinib at a dose of 100 mg QD.
- Additional systemic therapy is required for GVHD progression or lack of response, including corticosteroid doses greater than those used on Study Day 1.
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the Investigator's discretion)
- Inability of the patient to comply with study requirements
- Patient requests to discontinue treatment, but agrees to finish study procedures
- Patient withdraws consent from the study and is discontinued from the study
- Non-compliance/lost to follow-up
- Pregnancy
- Further participation would be injurious to the patient's health or well-being, in the Investigator's medical judgment.
- The study is terminated by the Sponsor or the Institutional Review Board (IRB).

After discontinuation from protocol treatment, patients must be followed for AEs for 30 days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the Investigator, these values are not likely to improve, because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patients' medical records.

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 5) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the Investigator, not likely that these values will improve. In this case, the Investigator must record his or her reasoning for making this decision in the patients' medical records.

4. STUDY REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, treatment alternatives, risks, and discomforts. Human protection committee (IRB) approvals of this protocol and any associated ICFs is required. Eligible patients who wish to participate in the study will be enrolled into the study.

Registration must occur prior to the initiation of protocol therapy. Patients eligible to participate in the study may be enrolled by each site following the patient registration instructions provided by the Sarah Cannon Development Innovations (Innovations) study contact. Patient registration follow-up and/or confirmation will be provided via email within approximately 24 hours or by the next business day.

5. STUDY DESIGN

This is an open-label, multi-center, single-arm pilot study in patients who have been receiving immunosuppressive therapy for the treatment of cGVHD for a duration of >6 months prior to starting daily itacitinib treatment in this study. The planned enrollment for this study is 40 patients, and patient treatment is expected to be approximately 12 months, although patients seeing clinical benefit may stay on treatment for an additional year.

Patients will continue to receive their systemic immunosuppressive regimen for SR-cGVHD per standard of care as determined by the Investigator during the screening and treatment periods. In addition, transfusion support, continued use of anti-infective medications, and topical steroid therapy is permitted.

Chronic GVHD staging and grading will be assessed for efficacy as per NIH Consensus Criteria (Jagasia et al. 2015). Safety and tolerability will be assessed as per NCI CTCAE Version 5.

5.1 Main Treatment Periods

Patients who taper off study treatment and all immunosuppressive therapy due to achieving a cGVHD status of CR or PR will continue to be followed according to the Schedule of Assessments (Appendix D), including all safety and efficacy assessments, and will be monitored for cGVHD recurrence.

5.1.1 Primary Efficacy Period (Cycle 1 through End of Cycle 6)

The primary efficacy period is defined as Cycle 1 through the end of Cycle 6. A cycle is 28 days. Study treatment will begin on Cycle 1 Day 1 and study drug will be dispensed on Day 1 of each cycle.

Patients will be treated for a minimum of 6 cycles, unless they meet the discontinuation criteria listed in Section 3.3).

Primary efficacy assessments will be performed on Cycle 7 Day 1, after completion of 6 cycles of treatment.

5.1.2 Extension Period (Cycle 8 to Cycle 12)

Patients will continue treatment and will be monitored on Day 1 of each cycle until the end-of-treatment (EOT) visit, according to the assessments outlined in Appendix D.

Patients undergoing dose tapering should be monitored for cGVHD flare occurrences, which must be reported in the database.

5.2 Treatments

5.2.1 Itacitinib

Itacitinib will be administered orally at a starting dose of 200 mg once QD (2 x 100 mg tablets), and may be taken with or without food.

Itacitinib dose will be increased to 300 mg QD (3 x 100 mg tablets) for patients with no response (NR)/stable disease (SD) after 2 months of therapy at 200 mg QD.

Patients may have dose reductions or interruptions of itacitinib during the course of treatment based on AEs, clinical evaluation, and laboratory assessments. See Section 8.1 for dose modifications of study drug.

5.2.2 Dietary Restrictions

Patients should be instructed to refrain from the consumption of pomegranates or pomegranate juice, and grapefruit or grapefruit juice, as these are known to inhibit cytochrome CYP3A enzymes and may increase exposure to itacitinib.

5.2.3 Corticosteroids

Patients will join this study after receiving immunosuppressive regimens for SR-cGVHD for at least 6 months and will remain on the dose at which they started if considered clinically appropriate by the Investigator.

Corticosteroids should be tapered per institutional guidelines at a rate that is commensurate with resolution of GVHD manifestations. If GVHD flares during the taper of prednisone or methylprednisolone, the dose may be re-escalated at the Investigator's discretion and will not be considered treatment failure, as long as the dose does not exceed the initial starting dose. If the dose required exceeds this threshold, or if the flare is not responsive to increased corticosteroids or multiple flares are observed, then the patient will be considered to have experienced treatment failure and will be withdrawn from study treatment.

5.3 Treatment Duration

While patients are expected to receive study treatment for approximately 1 year, those seeing clinical benefit may stay on treatment for an additional year.

Patients will be followed for survival for 1 year after the last dose of study drug. The total duration of the study is planned to be at least 3½ years.

5.4 Concomitant Medications

Patients will be instructed not to take any additional medications during the course of the study without prior consultation with the research team. At each visit, the patient will be asked about any new medications he/she is taking or has taken after the start of the study drug.

5.4.1 Permitted Concomitant Medications

Patients who undergo allo-HSCT are at risk for a variety of infections based on the degree of immunosuppression induced by the conditioning regimen before transplant. As such, it is considered routine practice to use antibiotics, anti-infectives, and immunizations as prophylactic therapies (Tomblyn et al. 2009). In cases where post-transplant anti-infective prophylaxis

measures are necessary, ongoing therapy may continue at the Investigator's discretion per institutional guidelines.

Additional supportive care measures (e.g., use of antimotility agents for diarrhea management, topical steroids) are permitted at the Investigator's discretion. Concomitant treatments and/or procedures that are required to manage a patient's medical condition during the study will be recorded in the eCRF.

5.4.2 Restricted Concomitant Medications

The following medications have restrictions on use during the treatment period of the study:

- Medications that interfere with coagulation or platelet function including, but not limited to, aspirin in doses exceeding 81 mg/day and related drugs such as heparin and warfarin sodium (Coumadin®) are not permitted. Low-dose aspirin (≤81 mg per day) is permitted, unless clinically contraindicated, as is the use of low molecular weight heparin. If concomitant administration of an anticoagulant/antiplatelet medication is indicated, then caution and enhanced monitoring is required; it is suggested that CBCs be checked every 1 to 2 weeks for the first 2 cycles of administration. History of thrombocytopenia should be a factor in the choice of anticoagulant and dose.
- For coadministration with potent CYP3A inhibitors; consider alternative agents with less CYP3A inhibition (Appendix J). Differences in individual sensitivity and varied CYP enzyme inhibition may result in the need for dose reduction of itacitinib and/or corticosteroids, as appropriate. **Note:** If the participant's medical condition requires treatment with any of these drugs, a dose reduction of itacitinib to 100 mg QD is recommended, as more potent inhibitors have been shown to increase exposure to itacitinib. No dose adjustment is recommended for concomitant administration of other CYP3A4 inhibitors.
- Coadministration with CYP3A4 inducers (Appendix J).

5.4.3 Prohibited Concomitant Medications

The following treatments are prohibited during the treatment period of the study:

- No other investigational therapy (e.g., chemotherapy, radiation therapy, surgery, immunotherapy [including other JAK inhibitors], biologic therapy, hormonal therapy, or tumor embolization) should be given to patients to treat a suspected malignancy relapse. If such agents are required for a patient, then the patient must first be withdrawn from the study.
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

6. STUDY ASSESSMENTS AND EVALUATIONS

6.1 Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedule of Assessments for this study is presented in Appendix D.

Safety laboratory assessments including hematology, serum biochemistry, pregnancy test, and urinalysis will be performed locally.

6.2 Baseline Study Assessments

The following information will be collected and procedures will be performed for each patient at screening. Screening should take place within 28 days of start of study treatment and safety laboratory assessments should be done within ≤14 days prior to initiation of treatment:

- Written informed consent prior to any other study-related procedures (see Section 13.3)
- Medical history and demographics
- Physical examination (including height and weight)
- ECOG performance status (see Appendix A)
- Vital signs (pulse rate, blood pressure [BP], and body temperature)
- Blood transfusion review
- 12-lead electrocardiogram (ECG)
- Pulmonary function tests (FEV1, FVC, DLCO, TLC, RV)
- Urine pregnancy test for women of child-bearing potential (must be performed within 72 hours prior to the start of treatment). Positive urine pregnancy test should be confirmed with a serum beta human chorionic gonadotropin (β-hCG) test.
- Hematology panel (hematocrit, hemoglobin, mean corpuscular volume, platelet count, red blood cell count, white blood cell [WBC] count, WBC 5-part differential)
- Clinical chemistry panel (sodium, potassium, phosphorus, chloride, creatinine, calcium, venous bicarbonate, albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total bilirubin, lactate dehydrogenase, serum glucose, and blood urea nitrogen)
- Lipid panel (fasting) (high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, total cholesterol, and triglycerides)
- Urinalysis
- Virology tests (HIV, Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, Hepatitis C antibody, HBV-DNA [if required], HCV-RNA [if required])
- Concomitant medication review

- AE and infection monitoring. Patients with either pre-transplant positive serology results or unknown viral testing results prior to transplant must have viral load results confirming no evidence of active viral infection within 28 days prior to study treatment.
- cGVHD diagnosis and staging (see Appendix G)
- Chimerism assessment as per institutional standards
- Lee Symptom Scale (see Appendix I)
- Document corticosteroid dosage (total dose/kg and type of corticosteroids)
- Document concomitant cGVHD therapy

6.3 Study Assessment Timing

The treatment period begins on the day the patient receives the first dose of study drug through the point at which the Investigator determines the patient will be permanently discontinued from study drug. Dates for subsequent study visits will be determined based upon this day and should occur as close to the scheduled day as possible taking into consideration the windows of time included in the assessments table. During the Day 1 visit, results from screening visit evaluations should be reviewed to determine whether the patient continues to meet the eligibility requirements as specified in the protocol.

6.3.1 Day 1 of Each Cycle

- Physical examination
- ECOG performance status
- Vital signs (blood pressure, body temperature, and pulse rate after about 5 minutes of rest)
- Blood transfusion review
- Hematology, lipid (fasting), and clinical chemistry panels
- Urinalysis
- Pulmonary function tests at Cycle 4 Day 1 and Cycle 7 Day 1 only (FEV1, FVC, DLCO, TLC, RV)
- Urine pregnancy test for women of child-bearing potential (testing is not required if done within 72 hours prior to the start of treatment on Cycle 1 Day 1). Positive urine pregnancy test should be confirmed with a β-hCG serum test.
- Concomitant medication review
- AE and infection monitoring
- Global cGVHD activity assessments (clinician-reported [Appendix E] and patient-reported [Appendix F])
- cGVHD response assessment (Appendix H) (starting at Cycle 2 through 7, and then every odd-numbered cycle thereafter starting with Cycle 9)

- Lee Symptom Scale (Day 1 of Cycles 1 and 7 only; Appendix I)
- Document corticosteroid dosage (total dose/kg and type of corticosteroids)
- Assess relapse of underlying malignancy (at the Investigator's discretion; formal re-staging not required)
- Document concomitant cGVHD therapy
- Dispense study drug, collect unused drug from previous cycle, and check compliance.

6.3.2 Days 8, 15, and 22 of Cycle 1 Only

- Physical examination
- Vital signs (blood pressure, body temperature, and pulse rate after about 5 minutes of rest)
- Hematology, lipid (fasting), and clinical chemistry panels
- Urinalysis
- Concomitant medication review
- AE and infection monitoring
- Document corticosteroid dosage (total dose/kg and type of corticosteroids)
- Document concomitant cGVHD therapy

6.4 Response Assessments

Response criteria (CR, PR, or other [unchanged, mixed response, progression]) based on the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD (see Appendix H for criteria) will be assessed on Day 1 of Cycles 2 through 7; and then every odd-numbered cycle thereafter starting on Day 1 of Cycle 9, as well as the EOT visit.

Patients with GVHD progression, progression of the underlying malignancy, or unacceptable toxicity should be discontinued from the study; patients with stable GVHD or a GVHD response to therapy will continue treatment.

6.5 End-of-Treatment Visit

The follow-up evaluations required after treatment ends (due to the completion of the planned study treatment period, GVHD progression, progression of underlying malignancy, or once the patient is discontinued due to unacceptable toxicity or the decision to discontinue treatment by the patient or the study physician) are specified in Appendix D. This visit should be performed within 7 days and no later than 14 days after discontinuation of study treatment. If treatment is discontinued because of toxicity or any other reason(s) and no study treatment is administered, that visit may fulfill the EOT visit.

The following assessments will be performed at the EOT visit:

- Physical examination

- ECOG performance status
- Vital signs (blood pressure, body temperature, and pulse rate after about 5 minutes of rest)
- Urine pregnancy test for women of child-bearing potential
- Blood transfusion review
- Electrocardiogram
- Hematology, lipid (fasting), and clinical chemistry panels
- Urinalysis
- Concomitant medication review
- AE and infection monitoring
- Global cGVHD activity assessment (clinician-reported [Appendix E] and patient-reported [Appendix F])
- cGVHD response assessment (Appendix H)
- Assess relapse of underlying malignancy with Lee Symptom Scale (Appendix I)
- Document corticosteroid dosage (total dose/kg and type of corticosteroids)
- Document concomitant cGVHD therapy

6.6 Follow-up

6.6.1 Safety Follow-Up (30 [±7] Days Following Last Dose of Study Treatment)

A 30-day safety follow-up assessment will be performed after the last dose of itacitinib.

The following assessments will be performed at this visit:

- Physical examination
- ECOG performance status
- Vital signs (blood pressure, body temperature, and pulse rate after about 5 minutes of rest)
- Hematology, lipid (fasting), and clinical chemistry panels
- Urinalysis
- Urine pregnancy test for women of child-bearing potential
- Concomitant medication review
- AE and infection monitoring
- Discuss new GVHD therapies

6.6.2 Survival Follow Up (Every 3 Months [±30 Days])

Patients who permanently discontinue the study treatment for reasons other than achieving a GVHD status of CR or PR will be followed for survival, relapse of underlying malignancy, and reporting of new cGVHD therapies approximately every 3 months for 1-year after completion of study drug, and can be contacted by telephone, email, or by a site visit.

6.7 Study Treatment Assessments

6.7.1 Informed Consent

All subjects must take part in the informed consent process. Adequate time must be allowed for the subject to ask questions and make a voluntary decision. No protocol-specific procedures, including screening procedures are to be performed until the subject has signed and dated an IRB-approved informed consent form (ICF). For more details, please see Section 13.3.

6.7.2 Medical History and Demographics

A complete medical history and demographics will be taken at screening. Information to be documented includes, prior medical illnesses and conditions, conditioning regimen, stem cell source, GVHD prophylaxis therapy, disease status at transplant, prior lines of GHVD therapy and surgical procedures.

6.7.3 Physical Examinations (Including Performance Scale and Vital Signs)

A complete physical examination will be done at screening, on Days 1, 8, 15, and 22 of Cycle 1, on Day 1 of each subsequent treatment cycle, at the end-of-treatment (EOT) and 30-day safety follow-up (FU) visits, and at the discretion of the Investigator. They will include documentation of height (screening only), weight, and vital signs collected after the patient has been sitting for at least 5 minutes (blood pressure, body temperature, and pulse rate). Blood transfusions will be reviewed at screening, Day 1 of each cycle and at the EOT visit. The ECOG performance status (see Appendix A) will be done at all visits with a physical exam with the exception of Days 8, 15, and 22 of Cycle 1. Any abnormal or clinically significant findings from the physical examination must be recorded on the appropriate electronic case report form (eCRF) page.

If these assessments are performed within 72 hours of initiation of treatment at the screening visit, an abbreviated physical examination can be done on Day 1 of Cycle 1. Vital signs assessments and ECOG performance status are still required prior to first study drug dose.

6.7.4 Pulmonary Function Test

Pulmonary function test will be performed at screening (within 14 days of Cycle 1 Day 1), Day 1 of Cycle 4 and Cycle 7 and include FEV1, FVC, DLCO (corrected for Hb), TLC and RV.

6.7.5 12-Lead Electrocardiogram

Electrocardiograms will be done at screening, at the EOT visit, and at the discretion of the Investigator. Each will be performed with the patient in a supine position having rested in this position for at least 5 minutes before the reading.

ECG should to be performed immediately prior to any blood sample collections, if possible.

6.7.6 Pregnancy Testing

Women of child-bearing potential will have a urine pregnancy test at screening (3 days prior to initiation of treatment), on Day 1 of each cycle, the EOT visit, and during the 30-day follow-up visit. Additional urine pregnancy testing is at the Investigator's discretion. Positive results are to be confirmed with serum beta human chorionic gonadotropin testing.

6.7.7 Laboratory Assessments

Laboratory samples (hematology, lipids [fasting], clinical chemistry, urinalysis, and virology [screening and as clinically indicated]) are to be collected as outlined in Appendix D. Safety laboratory analyses will be performed. Laboratory results will be graded using NCI CTCAE Version 5.

6.7.8 Chimerism Testing

Chimerism will be tested at screening according to institutional standards.

6.7.9 Response and Activity Assessments

Please see Section 9.

6.7.10 Prior and Concomitant Medications

All concomitant medications are to be collected and recorded in the eCRF from the time the patient signs the ICF throughout the patient's participation in the study.

6.7.11 Adverse Event Assessments

Information regarding the occurrence of AEs (including infections) will be collected from the time the patient signs the ICF throughout their participation in the study, including a period of 30 days after the last dose of study drug. Adverse event severity will be determined using the CTCAE Version 5 grading scale. Please see Section 11 for more details.

7. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

7.1 Itacitinib

Investigational Product	Dosage Form and Strength	Manufacturer
Itacitinib	100 mg	Incyte

Itacitinib 100 mg (free base equivalent) sustained-release tablets contain the active ingredients hypromellose, microcrystalline cellulose, lactose monohydrate, and magnesium stearate.

Itacitinib will be administered orally at a starting dose of 200 mg once QD (2 x 100 mg tablets), and may be taken with or without food.

Itacitinib dose will be increased to 300 mg QD (3 x 100 mg tablets) for patients with NR/SD after 2 months of therapy at 200 mg QD.

Patients may have dose reductions or interruptions of itacitinib during the course of treatment based on AEs, clinical evaluation, and laboratory assessments. See Section 8.1 for dose modifications of study drug.

Patients are permitted to remain on itacitinib treatment until withdrawal from study treatment is considered necessary as per Section 3.3.

7.1.1 Labeling, Packaging, and Supply

Incyte Corporation will provide itacitinib tablets to the sites in high-density polyethylene bottles. All Incyte Corporation investigational product labels will be in the local language and will comply with legal requirements.

At each visit, patients will be dispensed sufficient supplies until the next visit. Study drug compliance will be assessed at each patient visit. The research staff will count and document the amount of study drug taken and returned by the patient. The batch number of the study drug dispensed to the patient should be entered on the CRF, if applicable.

The immediate packaging will contain a statement to conform with U.S. Food and Drug Administration (FDA) Investigational New Drug (IND) requirements as follows: Caution: New Drug - Limited by Federal (or United States) law to investigational use.

All study drugs must be kept in a secure place under appropriate storage conditions.

Itacitinib should be stored at ambient conditions (15°C to 30°C, or 59°F to 86°F) per the IB.

Sarah Cannon Development Innovations (Innovations) representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

7.1.2 Preparation and Administration of Itacitinib

Itacitinib is administered orally. No preparation is required.

7.1.3 Instructions for Patients for Handling Itacitinib

Patients must be instructed in the handling of itacitinib as follows:

- To store the bottles at room temperature, in a safe place and out of the reach of children
- To only remove the number of tablets needed at the time of administration
- Not to remove tablets in advance of the next scheduled administration
- To make every effort to take doses on schedule
- To report any missed doses
- To take tablets with a glass of water
- Not to take another dose if vomiting occurs after taking the study medication, but rather wait for the next scheduled dose.
- On days of clinic visits, tablets can be taken before the visit or at the clinic after blood samples are collected.
- To bring all used and unused bottles of study medication to the site at each visit.

If the patient misses a dose of study drug, the patient should take the dose as soon as possible. If the next dose is due in less than 12 hours, however, the patient should skip the missed dose and take the next dose as scheduled.

If vomiting is persistent, the patient should contact the Investigator.

Study drug will be dispensed and compliance will be assessed by pill counts on Day 1 of each cycle. The research staff will count and document the amount of study drug taken and returned by the patient.

7.2 Corticosteroids

Patients will join this study after receiving immunosuppressive regimens of corticosteroids for SR-cGVHD for at least 6 months and will remain on the dose at which they started if considered clinically appropriate by the Investigator.

Corticosteroids should be tapered per institutional guidelines at a rate that is commensurate with resolution of GVHD manifestations. If GVHD flares during the taper of prednisone or methylprednisolone, the dose may be re-escalated at the Investigator's discretion and will not be considered treatment failure, as long as the dose does not exceed the initial starting dose. If the dose required exceeds this threshold, or if the flare is not responsive to increased corticosteroids or multiple flares are observed, then the patient will be considered to have experienced treatment failure and will be withdrawn from study treatment.

Corticosteroids may be taken or administered without food.

7.2.1 Prednisone

Prednisone is a white to off-white, odorless, crystalline powder. Tablets are typically white in color and contain lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate. Commonly available dose strengths include 1, 2.5, 5, 10, 20, and 50 mg tablets. Prednisone tablets should be stored in accordance with local prescribing information requirements.

Investigators are responsible for ensuring that patients receive commercially available supplies of prednisone for the duration of the study treatment period, if applicable.

7.2.2 Methylprednisolone

Methylprednisolone sterile powder is an anti-inflammatory glucocorticoid, which contains methylprednisolone sodium succinate as the active ingredient. Methylprednisolone sodium succinate (USP) is the sodium succinate ester of methylprednisolone, and it occurs as a white, or nearly white, odorless hygroscopic, amorphous solid. It is very soluble in water and in alcohol. Methylprednisolone (unreconstituted product or solution) should be stored in accordance with local prescribing information.

Investigators are responsible for ensuring that patients receive commercially available supplies of methylprednisolone for the duration of the study treatment period, if applicable.

7.3 Accountability for All Study Drugs

The Principal Investigator (or designee) is responsible for accountability of all used and unused study drug supplies at the site.

All study drug inventories must be made available for inspection by the Sponsor (Innovations) or its representatives and regulatory agency inspectors upon request.

At the end of the study, all Innovations Drug Accountability Record Form(s) will be completed by the site and sent to the Innovations Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by Innovations or its representative. Please contact Innovations regarding disposal of any study drug reserves.

8. DOSE MODIFICATIONS

Patients receiving itacitinib at a dose of 200 mg QD may have their dose reduced to 100 mg QD. Patients who are unable to tolerate itacitinib at a dose of 100 mg QD should be withdrawn from study treatment (see Table 1).

8.1 Criteria and Procedures for Dose Interruptions and Adjustments of Itacitinib

If toxicity occurs, the toxicity will be graded utilizing the NCI CTCAE Version 5 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE), and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Dose interruptions and modifications may occur for individual study patients based on the emergence or resolution of toxicity.

Treatment with itacitinib may be delayed up to 14 days to allow for resolution of toxicity. Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the Investigator, would make the patient unsuitable for further participation in the study. The Investigator should contact the Study Chair to discuss cases where treatment has been delayed for more than 14 days before restarting treatment.

Because patients may enter the study with compromised bone marrow function, these dose reductions are provided as guidelines (see Table 2). Individual decisions regarding dose reduction should be made using clinical judgment and in consultation with the Study Chair, taking into account relatedness of the AE to the study drug and the patient's underlying condition. Adverse events that have a clear alternative explanation or transient (≤72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules.

Table 1 Dose Levels of Itacitinib

Dose Level	Itacitinib
Dose Level +1[a]	300 mg QD
Starting Dose	200 mg QD
Dose Level -1	100 mg QD
Dose Level -2	Discontinue

a Itacitinib dose will be increased to 300 mg QD (3 x 100 mg tablets) for patients with NR/SD after 2 months of therapy at 200 mg QD

NR = no response; QD = once daily; SD = stable disease

Table 2 Guidelines for Interrupting and Restarting of Itacitinib

Adverse Event	Action Taken
Chemistry	
AST and/or ALT >3.0 × ULN in patients with normal ALT/AST at baseline	• **Interrupt** for up to 14 days until the toxicity has resolved to ≤ Grade 1. Exceptions require Sponsor approval. • **Restart** at previous dose. If assessed as related to itacitinib, restart at next lower dose and monitor as clinically indicated. **NOTE**: In patients with GVHD-related chemistry elevations at baseline, contact the Study Chair to discuss clinical management and possible dose reductions.
Total bilirubin elevations that occur in the presence of GVHD response that cannot be attributed to new liver GVHD or concomitant therapy	Total bilirubin is 3.0 to 5.0 x ULN: • **Repeat** assessment within 7 days. If elevation persists: – **Immediately hold or reduce** dose by 1 level until bilirubin ≤1.5 x ULN – **Re-escalate or resume** previous dose if the repeat value obtained 7 days later shows no persistent elevation. Total bilirubin is >5.0 to 10.0 x ULN: • **Repeat** assessment within 7 days. If elevation persists: – **Immediately interrupt** until bilirubin is ≤1.5 x ULN. – **Monitor** liver function tests weekly or more frequently as appropriate. – **Re-escalate or resume** previous dose if the repeat value obtained 7 days later shows no persistent elevation. Total bilirubin is >10.0 x ULN: • **Repeat** assessment within 7 days. If elevation persists:

Table 2 Guidelines for Interrupting and Restarting of Itacitinib

Adverse Event	Action Taken
	– **Interrupt** until bilirubin is ≤1.5 x ULN. – **Re-escalate or resume** at reduced dose if the repeat value obtained 7 days later shows no persistent elevation; if >7 days, discontinue treatment and monitor as appropriate.
Total bilirubin elevations that occur in patients with Stage 1/2 liver GVHD that cannot be attributed to worsening liver GVHD or concomitant therapy	Total bilirubin is >3.0 x ULN: • **Repeat** assessment within 7 days. If elevation persists: – **Reduce** dose by 1 dose level. – **Resume** previous dose if bilirubin is ≤3.0 x ULN.
Hematology	
ANC is <0.5 x 10^9/L, suspected as unrelated to study treatment (e.g., GVHD, active cytomegalovirus viremia)	• **Reduce** dose by 1 dose level. • **Monitor** ANC count as clinically indicated. • **Resume** previous dose if ANC count is ≥0.5 x 10^9/L for more than 7 days.
ANC is <0.5 x 10^9/L, suspected as related to study treatment	• **Interrupt** for up to 14 days. • **Monitor** ANC count as clinically indicated. • **Resume** at a reduced dose if ANC count is ≥0.5 x 10^9/L for more than 7 days. If the patient's ANC count remains at ≥0.5 x 10^9/L for more than 7 days after resuming treatment at a lower dose, the previous dose may be resumed.
Platelet count is <10 x 10^9/L, or platelet count has decreased by ≥50% from baseline, suspected as unrelated to study treatment	• **Reduce** dose by 1 dose level. • **Monitor** platelet count as clinically indicated. • **Resume** at previous dose if platelet count returns to ≥20 x 10^9/L for more than 7 days.
Platelet count is <10 x 10^9/L, or platelet count has decreased by ≥50% from baseline, suspected as related to study treatment	• **Interrupt** for up to 14 days. • **Monitor** platelet count as clinically indicated. • **Resume** at a reduced dose if platelet count returns to ≥20 x 10^9/L for more than 7 days. If the patient's platelet count remains at ≥20 x 10^9/L for an additional 7 days, the previous dose of may be resumed.
Other Toxicities	
Any Grade 1 or Grade 2 toxicity	• **Continue** treatment and manage the toxicity. • **Monitor** as clinically indicated.
Any Grade 3 toxicity, if clinically significant and not manageable by supportive care	• **Interrupt** up to 14 days until toxicity resolves to ≤ Grade 1. • **Restart** at same dose; if assessed as related to itacitinib, restart at next lower dose and monitor as clinically indicated.
Any recurrent Grade 3 toxicity at 100 mg	• **Discontinue** study treatment; follow-up per protocol.

Table 2 Guidelines for Interrupting and Restarting of Itacitinib

Adverse Event	Action Taken
QD dose	Exceptions require Study Chair approval.
Any other Grade 4 toxicity	• **Discontinue** study treatment; follow-up per protocol.

ALT = alanine aminotransferase; Absolute neutrophil count = ANC; AST = aspartate aminotransferase; GVHD = graft versus host disease; LFT = liver function test; ULN = upper limit of normal.

8.2 Adjustments of Corticosteroids

Adjustments or tapering of the dose of corticosteroids should be made at the treating Investigator's discretion.

8.3 Tapering of Itacitinib

If a patient has achieved CR or PR after 6 months of treatment, Investigators may begin to taper the dose of itacitinib by 1 dose level provided corticosteroids have been discontinued for at least 8 weeks following institutional guidelines. Subjects must not be experiencing any Grade 2 or higher hematologic toxicity related to study treatment or symptoms of an active infection.

Investigators wishing to initiate a taper of itacitinib at an earlier time point may do so upon consultation with and approval from the Study Chair.

If GVHD signs/symptoms worsen during the taper of itacitinib, the dose may be escalated by 1 dose level. If the patient requires additional systemic therapy (includes restarting of corticosteroids), then the patient would be considered as having disease progression (PD) and would be withdrawn from study treatment.

8.4 Criteria for Permanent Discontinuation of Itacitinib

A full list of criteria for permanent discontinuation of itacitinib are presented in Section 3.3.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response will be evaluated by determining the ORR after 6 months of treatment with itacitinib as defined by NIH Consensus Criteria. In addition, patients' ability to either withdraw or decrease steroids while receiving itacitinib will be evaluated, as will patients' personal assessment of their quality of life.

9.1 2014 NIH Consensus Development Project on Clinical Trials in cGVHD

Patient response (CR, PR, or other [unchanged, mixed response, progression]) based on the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD is the primary activity endpoint for this study (see Appendix H for criteria). Response criteria will be assessed on Day 1 of Cycles 2 through 6, between the end of Cycle 6 and the start of Cycle 7, every odd-numbered cycle thereafter starting with Cycle 9, and at the EOT visit.

9.2 Clinician-Reported and Patient-Reported Global cGVHD Activity Assessments

Patients will be assessed for severity of cGVHD using the Clinician-Reported Global cGVHD Activity Assessment Form (Appendix E) and Patient-reported cGVHD Activity Assessment Form (Appendix F). Chronic GVHD severity will be assessed on Day 1 of each cycle and at the EOT visit.

9.3 Corticosteroid Use

Corticosteroid dose will be collected throughout the study according to the Schedule of Assessments (Appendix D) and changes will be documented. Please see Section 7.2 for additional details.

9.4 Quality-of-Life Impact

Quality of life impact will be assessed according to the Schedule of Assessments (Appendix D) using the Lee Symptom Scale (see Appendix I; Lee et al. 2002).

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This is a multi-center, open-label, single-arm pilot study of itacitinib in patients who have been receiving immunosuppressive therapy for the treatment of SR-cGVHD for a duration of >6 months prior to starting daily itacitinib treatment in this study. The study is designed to determine the ORR after 6 months of treatment with itacitinib.

10.2 Sample Size Considerations

No formal hypothesis testing is planned for this exploratory trial. In order to estimate the ORR in this population, a 95% exact two-sided confidence interval (CI) will be calculated. A sample size of 40 produces a two-sided 95% CI with a width equal to 0.266 when the sample proportion is 0.200 (i.e., 20% response rate).

10.3 Analysis Population

The following analysis populations will be used:

- The Response Evaluable Analysis Set is defined as all patients with cGVHD who received at least one cycle of itacitinib and completed at least one post-baseline disease assessment.
- The Safety Analysis Set is defined as all patients who received at least one dose of itacitinib.

10.4 Data Analysis

Descriptive statistics, including mean, median, standard deviations and ranges for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. Time-to-event endpoints will be reported using Kaplan-Meier estimates, with 95% CIs for median time to event.

10.4.1 Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized using descriptive statistics. Data to be tabulated will include demographic features such as age, sex, and race, as well as disease-specific characteristics.

The number and percentages of patients enrolled, treated, completed the treatment/study and withdrawn from treatment/study for any reason will be presented.

10.4.2 Efficacy Analysis

All efficacy analyses will be performed using the Response Evaluable Analysis Set.

- ORR is defined as the proportion of patients with a cGVHD status of CR or PR after 6 months of treatment according to the NIH Consensus Criteria (Lee et al. 2015.

- Overall Survival (OS) is defined as the time from the first day of study drug administration (Day 1) to death on study. Patients who are alive will be censored at the date of last known date alive.

For ORR, the estimates and the associated 95% CIs (based on the Clopper-Pearson method) will be calculated.

For OS, a Kaplan-Meier curve will be generated and the median time to event and the associated 95% CIs will be provided.

10.4.3 Safety Analysis

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy, and will be graded according to NCI CTCAE Version 5. A copy of CTCAE scoring system may be downloaded from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0_2010-06-14_QuickReference_8.5x11.pdf.

The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized using system organ class and preferred term for all patients in the Safety Analysis Set. In addition, summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be presented.

Other safety endpoints including laboratory results, vital signs, ECG findings, and other protocol-specified tests will be listed and/or summarized for all patients in the Safety Analysis Set.

Concomitant medications will be coded using the World Health Organization-Drug Dictionary and they will be listed and summarized.

10.5 Analysis Time Points

10.5.1 Final Analysis

The final analysis of the study will occur following the last visit of the last patient.

10.5.2 Safety Review

The clinical trial will be placed on hold if itacitinib is discontinued due to AEs in greater than 5/10, 10/20, or 15/30 patients.

10.5.3 Efficacy Analysis

The primary efficacy analysis will be done on consolidated data following 6 months of treatment (between the end of Cycle 6 and the beginning of Cycle 7).

11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and serious AEs (SAEs), measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables, and measurement of protocol-specified vital signs and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Principal Investigator is responsible for recognizing and reporting AEs to the SC Innovations Safety Department (see Section 11.1.5). It is Innovations' responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of each IRB.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

11.1 Definitions

11.1.1 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE (also known as adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose (including overdose).

11.1.2 Serious Adverse Events

An AE or a suspected adverse reaction (SAR) is considered "serious" if it results in any of the following outcomes:

- **Death**
- **A life-threatening AE**
- **Inpatient hospitalization or prolongation of an existing hospitalization**
- **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
- **A congenital anomaly/birth defect**

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

It is important to distinguish between "serious" and "severe" when describing AEs, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. Seriousness serves as the guide for defining regulatory reporting obligations. "Serious" is a regulatory definition and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

11.1.3 Adverse Reaction

An adverse reaction means any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is a reason to conclude that the drug caused the event.

11.1.4 Suspected Adverse Reaction

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

11.1.5 Recording and Reporting of Adverse Events

11.1.5.1 Recording of Adverse Events

All AEs will be recorded in the eCRF for all patients during the course of the research study, and the Investigator will give his or her opinion as to the relationship of the AE to the study treatment (i.e., whether the event is related or unrelated to study drug administration).

A description of the event, including its date of onset and resolution, whether it constitutes a SAE or not, any action taken (e.g., changes to study treatment), and outcome, should be provided, along with the Investigator's assessment of causality (i.e., the relationship to the study treatment). For an AE to be a suspected treatment-related event there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE Version 5, and changes will be documented.

If the AE is serious, it should be reported immediately to the Innovations Safety Department. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-

mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms; abnormal test findings; changes in physical examination; hypersensitivity; and other measurements that occur will be reported as an AE, and collected on the relevant eCRF screen.

Test findings will be reported as an AE if the test result requires an adjustment in the study drug(s) or discontinuation of treatment; and/ or test findings require additional testing or surgical intervention; a test result or finding is associated with accompanying symptoms; or a test result is considered to be an AE by the Investigator.

11.1.5.2 Reporting Period for Adverse Events

All AEs regardless of seriousness or relationship to the study treatment spanning from the signing of the informed consent form until 30 calendar days after discontinuation or completion of study treatment, as defined by this clinical study protocol, are to be recorded on the corresponding screen(s) included in the eCRF.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the Investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patient's medical record.

After 30 days of completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the Investigator as treatment-related are to be reported.

11.1.6 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, Investigators should apply the following general guideline:

> **YES:** There is a plausible temporal relationship between the onset of the AE and administration of the study medication, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies, and/or the AE follows a known pattern of response to the study drug, and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
>
> **NO:** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

11.2 Serious Adverse Event Reporting by Investigators

Adverse events classified by the treating Investigator as serious require expeditious handling and reporting to the Innovations Safety Department in order to comply with regulatory requirements. Determination of life-threatening or serious is based on the opinion of the Investigator.

Serious AEs may occur at any time from the signing of the informed consent form through the 30-day follow-up period after the last dose of study drug. **The Innovations Safety Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.**

To report an SAE, the SAE Report Form should be completed with the necessary information.

The SAE report should be sent to the Innovations Safety Department via fax or e-mail using the using the following contact information (during both business and non-business hours):

Sarah Cannon Innovations Safety Department

Safety Dept. Fax #: 1-866-807-4325

Safety Dept. Email: CANN.SAE@SCRI-Innovations.com

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the Innovations Safety Department as soon as it is available; these reports should be submitted using the Innovations SAE Report Form.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB.

11.3 Recording of Adverse Events and Serious Adverse Events

11.3.1 Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF screen). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as an SAE.

11.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE

eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF screen.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF screen.

11.3.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF screen. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF screen.

Abnormal laboratory values will be reported as an AE if the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment and/ or laboratory findings require additional testing or surgical intervention, a laboratory result or finding is associated with accompanying symptoms; or a laboratory result is considered to be an AE by the Investigator.

11.3.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed solely to progression of disease, as determined by the Investigator, will be recorded on the "End of Study" eCRF screen. All other on-study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the Innovations Safety Department.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and Adverse Event eCRF screen. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" (death, cause unknown) on the eCRF Adverse Event screen. During post-study survival follow-up, deaths attributed to progression of disease will be recorded only on the "Follow-Up Summary" and "Death Page" eCRF screens.

11.3.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolongation of pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility

- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as an SAE to the Innovations Safety Department.

11.3.6 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History eCRF screen. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF screen, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.3.7 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria (see Section 11.1.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.3.8 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form should be completed and faxed to the Innovations Safety Department. The Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Innovations Safety Department.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the Innovations Safety Department immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

11.3.9 Itacitinib Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Innovations Safety Department no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting (see Section 11.2).

There has been no clinical experience with over dosage of itacitinib. The highest total daily dose evaluated in clinical studies was 1200 mg (600 mg twice daily). No unexpected TEAEs were associated with doses of this level. Treatment of a suspected overdose with itacitinib should consist of general supportive measures, as needed.

For information on how to manage an overdose of itacitinib, see the IB.

11.4 Incyte Corporation Serious Adverse Event Reporting Requirements

The Innovations Safety Department will forward SAE information to Incyte's Pharmacovigilance (PhV) Department via email (IncytePhVOpsIST@incyte.com) within 1 business day of the Innovations Safety Department personnel becoming aware of the SAE.

If necessary, the Incyte PhV representative or designee will query the Innovations Safety Department (within 48 hours of receipt) for additional information to ensure a valid case prior to distributing the report for internal Incyte review.

Innovations is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating Investigators, in accordance with International Conference on Harmonisation (ICH) guidelines, and FDA regulations.

Incyte in turn will report relevant events originating from this study to the applicable Incyte IND(s) and will distribute Investigator Notifications to Investigators participating in the applicable Incyte IND(s).

11.4.1 Sponsor Assessment of Unexpected Events

The Sponsor is responsible for assessing an AE or suspected AE as "unexpected".

An AE or suspected adverse reaction is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the IB (or current US Package Insert [USPI])
- Event(s) is not listed at the specificity or severity that has been observed
- An event(s) is not consistent with the General Investigative Plan or in the current application
- Includes AEs or SAR that may be anticipated from the pharmacological properties of the study drug, or that occur with members of the drug class, but that have previously been observed under investigation.

Known as Suspected Unexpected Serious Adverse Reactions (SUSAR), these events suspected (by the Investigator or Sponsor) to be related to the study drug, are unexpected (not listed in the Investigator's Brochure or USPI), and are serious (as defined by the protocol) and require expedient submission to relevant health authorities within 7 days (fatal or life-threatening events) or 15 days (all serious events), or as defined by law. The term SUSAR is used primarily in the reporting of events to regulatory authorities.

Expected AEs are those events that are listed or characterized in the current IB or current IB.

11.4.2 Funding Partner Reporting for Clinical Studies Under an Investigational New Drug Application

All written IND Safety Reports submitted to the FDA by the Innovations Safety Department must also be sent to the pharmaceutical company that is supporting the study with either funding or drug supply:

Incyte Corporation

IncytePhVOpsIST@incyte.com

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Study Monitoring, Auditing, and Inspecting

The Investigator will permit study-related monitoring, quality audits, and inspections by Incyte Corporation, or its representative(s), government regulatory authorities, and the IRB(s) of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The Investigator will ensure the capability for inspections of applicable study-related facilities. The Investigator will ensure that the study monitor or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At the discretion of Innovations, Source Document Verification (SDV) may be performed on all data items or a percentage thereof.

Participation as an Investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the IRB(s), and/or Innovations or its representative(s).

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and the Code of Federal Regulations (CFR) Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

13.1 Institutional Review Board Approval

The clinical study protocol, ICF, IB, available safety information, patient documents, patient recruitment procedures (e.g., advertisements), information about payments (i.e., Principal Investigator payments) and compensation available to the patients and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval prior to the study start.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going, IRB study review. The Principal Investigator/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF document. Investigators will be

advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for itacitinib, will be prepared by Incyte Corporation or its representative as required, for distribution to the Investigator(s) and submission to the relevant IRB.

13.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

13.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each ICF must include all of the relevant elements currently required by the FDA, as well as local country authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF, which will include the patient's signature, will be provided by the Investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to patients, the patient's must re-consent to continue participation in the study.

13.3.1 Confidentiality

13.3.1.1 Patient Confidentiality

Confidentiality of patients' personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws

- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the Investigator and institution permit authorized representatives of Innovations, the regulatory authorities, and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

One measure to protect confidentiality is that only a unique study number will identify patients in the eCRF or other documents submitted to Innovations. This information, together with the patient's year of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF. No material bearing a patient's name will be kept on file by Innovations. Patients will be informed of their rights within the ICF.

13.3.1.2 Investigator and Staff Information

Personal data of the Investigators and sub-Investigators may be included in the Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator or sub-Investigator, Innovations personnel shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

13.4 Financial Information

The finances for this clinical study will be subject to a separate written agreement between Sarah Cannon Development Innovations, LLC and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

14.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Study Chair/Sponsor. All amendments require review and approval of all pharmaceutical companies providing funding for the study and the Principal Investigator supporting the study.

The written amendment must be reviewed and approved by Innovations and submitted to the IRB at the Investigator's facility for the board's approval.

Items requiring a protocol amendment approval from the IRB and/or FDA or other regulatory authorities includes, but are not limited to, the following:

- Change to study design
- Risk to patients
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and/or procedures
- Addition/removal of a new Investigator

The amendment will be submitted formally to the FDA or other regulatory authorities by Innovations.

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patients' consent to continue participation in the study should be obtained.

14.2 Documentation Required to Initiate the Study

Before the study may begin, certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

Sarah Cannon Development Innovations
Regulatory Department
1100 Dr. Martin L. King Jr. Blvd.
Suite 800
Nashville, TN 37203

Documents at a minimum required to begin a study in the US include, but are not limited to the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current curricula vitae for the Principal Investigator and any associate Investigator(s) who will be involved in the study
- Indication of appropriate accreditation for laboratories (as required) to be used in the study and the normal ranges for tests to be performed by those laboratories
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB-approved consent form containing permission for audit by representatives of Innovations, the IRB, and the FDA and other regulatory agencies (as applicable)

- Financial disclosure forms for all Investigators listed on Form FDA 1572 (if applicable)
- Verification of Principal Investigator acceptability from local and/or national debarment list(s).

14.3 Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patient's eCRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patient's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The Principal Investigator and each study staff member is responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or Investigator study file [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed eCRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Principal Investigator name, date drug shipped/received, and the date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

Innovations shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRFs, medical records), all original, signed ICFs, and copies of all eCRFs, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor will notify the Investigator(s)/institutions(s) when the study-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the study, both the Sponsor and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to Innovations. The Investigator must obtain Innovations' written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by Innovations at the conclusion of the study.

14.4 Data Collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable Innovations to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, and year of birth will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Innovations and replaced instead with the patient number and other identifier (i.e. patient's initials) as allowed per institutional policy. The Investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested in the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or the result was "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The Investigator will electronically sign and date the patient eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the Principal Investigator, once all data for that patient is final.

14.5 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication process.

Inclusion of the Investigator in the authorship of any multi-center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the study. The Investigator acknowledges that the study is part of a multi-center study and agrees that any publication by the Investigator of the results of the study conducted at research site shall not be made before the first multi-center publication. In the event there is no multi-center publication within fifteen (15) months after the study has been completed or terminated at all study sites, and all data has been received, the Investigator shall have the right to publish its results from the study, subject to the notice requirements described herein and subject to acknowledgment of the Sponsor as appropriate. The Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the Investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any Innovations Confidential Information from all publications.

15. REFERENCES

Choi et al. 2012

Choi J, Ziga ED, Ritchey J, Collins L, Prior JL, Cooper ML, et al. IFNγR signaling mediates alloreactive T-cell trafficking and GVHD. Blood. 2012;8:4093-103.

Choi et al. 2014

Choi J, Cooper ML, Alahmari B, Ritchey J, Collins L, Holt M, et al. Pharmacologic blockade of JAK1/JAK2 reduces GVHD and preserves the graft-versus-leukemia effect. PLoS One. 2014;9:e109799.

Garnett et al. 2013

Garnett C, Apperley JF, Pavlů J. Treatment and management of graft-versus-host disease: improving response and survival. Ther Adv Hematol. 2013;4(6):366–78. doi: 10.1177/2040620713489842.

Itacitinib Investigator's Brochure

Shukla J. Itacitinib Investigator's Brochure Version 10. Indication: myeloproliferative neoplasms, inflammatory diseases, graft-versus-host disease, solid tumors, and B-cell malignancies. 01 February 2019.

Jagasia et al. 2015

Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biol Blood Marrow Transplant. 2015;21(3):389–01.

Lee et al. 2002

Lee SK, Cook EF, Soiffer R, Antin JH. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2002;8(8):444-52.

Lee et al. 2015

Lee SJ, Wolff D, Kitko C, Koreth J, Inamoto Y, Jagasia MH, et al. Measuring Therapeutic Response in Chronic Graft-Versus-Host Disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease: IV. The 2014 Response Criteria Working Group Report. Biol Blood Marrow Transplant. 2015;21:984–99.

Spoerl et al. 2014

Spoerl S, Mathew NR, Bscheider M, Schmitt-Graeff A, Chen S, Mueller T, et al. Activity of therapeutic JAK 1/2 blockade in graft-versus-host disease. Blood. 2014;123:3832-42.

Tomblyn et al. 2009

Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15:1143-38.

Zeiser et al. 2015

Zeiser R, Burchert A, Lengerke C, Verbeek M, Maas-Bauer K, Metzelder SK, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multi-center survey. Leukemia. 2015;29:2062–68.

16. APPENDICES

Appendix A: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death no imminent
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix B: New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

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

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix C: Guidelines for Female Patients of Childbearing Potential and Fertile Male Patients

Acceptable Contraception Methods:

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly-effective contraception during the study and until after the 30-day safety follow-up visit.

Highly effective contraception is defined as either:

True Abstinence When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Sterilization When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.

Male Partner Sterilization When the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.

Use of a combination of any 2 of the following (one from a + one from b):

a) Placement of an intrauterine device (IUD) or intrauterine system (IUS)

b) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential must use condoms plus a spermicidal agent during the study treatment period and until after the 30-day safety follow-up visit, and must not father a child during this period.

Male patients must also refrain from donating sperm during their participation in the study and for at least 3 months after completing the study.

The following are acceptable forms of barrier contraception:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

Unacceptable Contraception Methods: for women of childbearing potential include:

- IUD progesterone T
- Female condom

- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield.

Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to the Innovations Safety Department within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the Investigator to the Innovations Safety Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women Not Of Childbearing Potential Are Defined As Follows:

- Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms).
- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
- Women who are >45 years-of-age, not using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L).
- Women who are >45 years-of-age, using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone-replacement therapy.

Appendix D: BMT 29 Schedule of Assessments

Study Period	**Screening**	**Treatment Period**							**Follow-Up**		
Cycle[a]		**Cycle 1**				**Cycles 2 to 6**	**Cycle 7**	**Cycles 8+**	**EOT[k]**	**30-Day Safety FU[l]**	**FU for Survival[m]**
Visit Day	**Day -28 to -1[b]**	**1**	**8**	**15**	**22**	**1 (±7 days)**	**1 (±7 days)**	**1 (±7 days)**		**(±7 days)**	**Every 3 months (±1 month)**
Informed consent	X										
Inclusion / exclusion criteria	X										
Medical history and demographics[c]	X										
Physical examination[c,d]	X	X	X	X	X	X	X	X	X	X	
ECOG performance status[c,d]	X	X				X	X	X	X	X	
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	
Blood transfusion review[d]	X	X				X	X	X	X		
12-Lead electrocardiogram[c]	X								X		
Pulmonary function test[d]	X					X (C4 only)	X				
Urine pregnancy test[c,e]	X	X				X	X	X	X	X	
Safety laboratory (hematology, lipids [fasting], and chemistries)[c]	X	X	X	X	X	X	X	X	X	X	
Safety laboratory (urine)[c]	X	X	X	X	X	X	X	X	X	X	
Virology testing[f]	X										
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	
Adverse events and infection monitoring	X	X	X	X	X	X	X	X	X	X	
cGVHD diagnosis and staging	X										
Clinician-reported global cGVHD activity assessment[g]		X				X	X	X	X		

Study Period	Screening	Treatment Period							Follow-Up		
Cycle[a]		**Cycle 1**				**Cycles 2 to 6**	**Cycle 7**	**Cycles 8+**	**EOT[k]**	**30-Day Safety FU[l]**	**FU for Survival[m]**
Visit Day	**Day -28 to -1[b]**	**1**	**8**	**15**	**22**	**1 (±7 days)**	**1 (±7 days)**	**1 (±7 days)**		**(±7 days)**	**Every 3 months (±1 month)**
Patient-reported global cGVHD activity assessment[g]		X				X	X	X	X		
Assessment of cGVHD response (NIH criteria)[h]						X	X	X[h]	X		
Chimerism assessment (institutional standards)	X										
Lee Symptom Scale[i]	X	X					X		X		
Document corticosteroid dosage (total dose/kg and type of corticosteroid)	X	X	X	X	X	X	X	X	X		
Document concomitant cGVHD therapies	X	X	X	X	X	X	X	X	X		
Assess underlying disease relapse[j]		X				X	X	X	X		X
New cGVHD therapies										X	X
Dispense/collect study drug		X				X	X	X	X		
Patient status											X

Itacitinib Schedule of Assessments Footnotes

a Treatment cycles are 28 days (4 weeks). Patients will continue treatment with itacitinib for up to 24 months or until patients discontinue from study treatment for any of the following reasons listed in Section 3.3.

b Screening should take place within 28 days of start of study treatment.

c Safety laboratory assessments including hematology, lipids (fasting), clinical chemistry, pregnancy test, and urinalysis will be performed locally. Additional assessments to be performed during the screening period:

- Blood transfusion review
- Virology tests (HIV, Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, Hepatitis C antibody, HBV-DNA [if required], HCV-RNA [if required])

- Concomitant medication review
- cGVHD diagnosis and staging
- Chimerism assessment as per institutional standards
- Lee Symptom Scale
- Document corticosteroid dosage (total dose/kg and type of corticosteroids)
- Document concomitant cGVHD therapy

The following screening parameters should be done ≤14 days prior to initiation of treatment:

- Pulmonary function tests (FEV1, FVC, DLCO (corrected for Hb), TLC and RV)
- medical history and demographics (includes conditioning regimen, stem cell source, GVHD prophylaxis therapy, disease status at transplant and prior lines of GHVD therapy), physical examination (including height and weight), Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, electrocardiogram (ECG)
- **hematology:** hematocrit, hemoglobin, mean corpuscular volume, platelet count, red blood cell count, white blood cell (WBC) count, WBC 5-part differential
- **clinical chemistry (lipids in a fasting state):** sodium, potassium, phosphorus, chloride, creatinine, calcium, venous bicarbonate, albumin, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, lactate dehydrogenase, serum glucose, and blood urea nitrogen, lipids high-density lipoprotein (HD) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, and triglycerides
- **urinalysis**
- screening pregnancy test (urine)

If these assessments are performed within 72 hours of initiation of treatment, they do not need to be repeated on Cycle 1 Day 1 with the exception of the ECOG performance status, an abbreviated physical examination, and vital signs, which are required prior to first study dose. Vital signs (blood pressure, body temperature, and pulse rate) are checked at every visit prior to blood work and study treatment and at the discretion of the Investigator (see Section 6.7.3).

d Physical examinations including the measurements of height (screening only) and weight will be done at screening, on Days 1, 8, 15, and 22 of Cycle 1, on Day 1 of each subsequent treatment cycle, at the end-of-treatment (EOT) and the 30-day safety follow-up (FU) visits, and at the discretion of the Investigator. Blood transfusions will be reviewed at screening, on Day 1 of each cycle, and at the EOT visit. ECOG performance status will be done at the visits noted in the table. Pulmonary function test will be performed at screening (within 14 days of C1D1) and on Day1 of Cycle 4 and Cycle 7 and include FEV1, FVC, DLCO (corrected for Hb), TLC and RV (see Section 6.7.3).

e A urine pregnancy test must be done at screening (3 days prior to initiation of treatment) for women with child-bearing potential, Day 1 of each cycle, at the EOT visit, and at the 30-day safety follow-up visit. Additional pregnancy testing is at the Investigator's discretion. Positive results are to be confirmed with serum beta human chorionic gonadotropin testing.

f Virology tests to include: HIV, Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, Hepatitis C antibody, HBV-DNA (if required), HCV-RNA (if required)

g Patients will be assessed for severity of cGVHD using the Clinician-Reported Global cGVHD Activity Assessment Form (see Appendix E) and Patient-reported cGVHD Activity Assessment Form (Appendix F) on Day 1 of each cycle, and at the EOT visit. If a patient withdraws from treatment due to reasons other than PD, GVHD grading will be repeated at this visit.

h Response criteria (CR, PR, or progression) based on the 2014 NIH Consensus Development Project on Clinical Trials in cGVHD (see Appendix H for criteria) will be assessed on Day 1 of Cycles 2 through 7; and then every odd-numbered cycle thereafter starting on Day 1 of Cycle 9, as well as the EOT visit.

i The Lee Symptom Scale (see Appendix I) will be used to capture changes in health status during the course of treatment relative to screening and will be done at screening, on Cycle 1 Day 1, Cycle 7 Day 1, and at the EOT visit. If a patient stops study drug before 6 months, the form should be filled out at that time.

j Participants will be closely monitored for any evidence of underlying disease relapse or recurrence on Day 1 of each cycle, at the EOT, and the survival follow-up visit. A formal re-staging is not required. Re-staging will be done at the Investigator's discretion. The date of malignant and non-malignant hematologic disease relapse and subsequent management should be collected on the appropriate eCRF.

k An EOT visit should be performed for all patients who permanently discontinue study treatment (preferably within 7 days and no later than 14 days after the last treatment of study drug). If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF (see Section 6.5).

l A safety follow-up visit will be done 30 days (±7 days) following end of treatment. Adverse events and SAEs must be reported for least 30 days after the last dose of study drug, and must be followed until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer (see Section 6.6.1).

m Follow-up for survival: patients will be followed for survival after treatment has been discontinued. Patients should be contacted by telephone, email, or visit every 3 months for 1-year after their last dose of study treatment to assess for new GVHD therapy, relapse of underlying malignancy and survival status until death, withdrawal of consent, or the end of the study, whichever occurs first (see Section 6.6.2).

Appendix E: Clinician-Reported Global cGVHD Activity Assessment Form

SARAH CANNON
Development Innovations

Appendix: Clinician -Reported Global cGVHD Activity Assessment Form **BMT29**

Current Patient Weight: _____
Today's Date: _____
Cycle#/Visit #: _____

Subject ID#: _____

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Health Care Provider Global Ratings: 0=none 1= mild 2=moderate 3=severe	**Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:** 0 1 2 3 4 5 6 7 8 9 10 **cGvHD symptoms not at all severe** — **Most severe cGvHD symptoms possible**	**Over the <<time>> would you say that this patient's cGvHD is** +3= Very much better +2= Moderately better +1= A little better 0= About the same -1=A little worse -2=Moderately worse -3=Very much worse

Mouth	**Erythema**	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
	Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
	Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
				Total score for all mucosal changes					

Gastrointestinal-Esophageal • Dysphagia OR Odynophagia	*0= no esophageal symptoms* *1=Occasional dysphagia or odynophagia with solid food or pills during the past week* *2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week 3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week*
Gastrointestinal-Upper GI • Early satiety OR • Anorexia OR • Nausea & Vomiting	*0= no symptoms* *1=mild, occasional symptoms, with little reduction in oral intake during the past week 2=moderate, intermittent symptoms, with some reduction in oral intake during the past week* *3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week*
Gastrointestinal-Lower GI • Diarrhea	*0= no loose or liquid stools during the past week* *1= occasional loose or liquid stools, on some days during the past week* *2=intermittent loose or liquid stools throughout the day, on almost every day of the past week, **without requiring** intervention to prevent or correct volume depletion* *3=voluminous diarrhea on almost every day of the past week, **requiring** intervention to prevent or correct volume depletion*

Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1	FVC	Single Breath DLCO (adjusted for hemoglobin)		TLC	RV
Liver Values	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L	ULN U/L	Alkaline Phosphatase U/L	ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins: ❑ 2 min ❑ 6 min		Karnofsky or Lansky	PlateletCount K/uL	Total WBC K/uL	Eosinphils %
	❑ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____ ❑ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____ ❑ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause):_____					

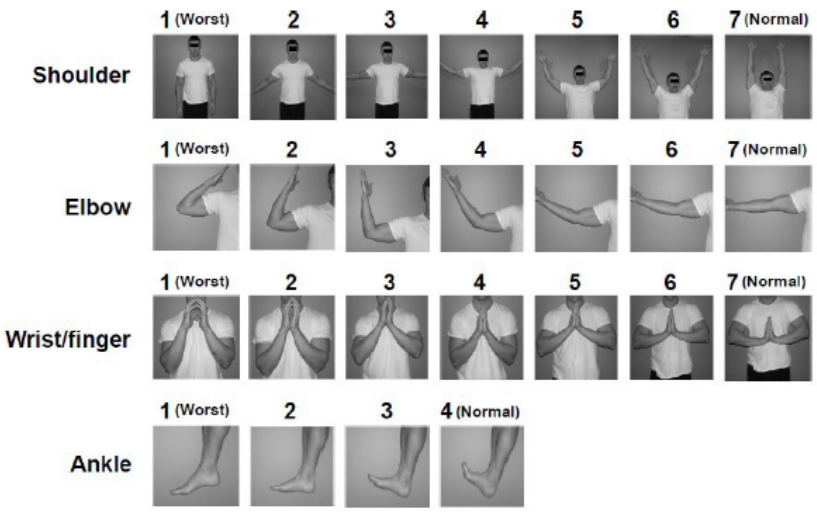
Reference: Lee et al. 2015

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN *GVHD features to be scored by BSA:* **Check all that apply:** ❑ Maculopapular rash erythema ❑ Lichen planus-like features ❑ Sclerotic features ❑ Papulosquamous lesions ichthyosis ❑ Keratosis pilaris-like	❑ No BSA involved	❑ 1-18% BSA	❑ 19-50% BSA	❑ >50% BSA
Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
SKIN FEATURES SCORE:	❑ No sclerotic features		❑ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ❑ Deep sclerotic features ❑ "Hidebound" (unable to pinch) ❑ Impaired mobility ❑ Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____ How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 Symptoms not at all severe — Most severe symptoms possible				
EYES	❑ No symptoms	❑ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	❑ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	❑ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
LUNGS	❑ No symptoms	❑ Mild symptoms (shortness of breath after climbing one flight of steps)	❑ Moderate symptoms (shortness of breath after walking on flat ground)	❑ Severe symptoms (shortness of breath at rest; requiring 0_2)
Abnormality present but explained entirely by non-GVHD documented cause (specify):				
JOINTS AND FASCIA	❑ No symptoms	❑ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	❑ Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	❑ Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

All abnormalities should be documented; however, the organ is not evaluable if there is another well-documented non-chronic GVHD cause.



❑ Not done

❑ Not done

❑ Not done

❑ Not done

Reference: Lee et al. 2015

Appendix F Patient-Reported Global cGVHD Activity Assessment Form

SARAH CANNON
Development Innovations

BMT29 Cycle#:_____ Patient ID:_____

Date:_____

Appendix: Patient-Reported Global cGVHD Activity Assessment Form

CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

Symptoms **Please rate how severe the following symptoms have been in the last seven days. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.**	**Not Present** 0	1	2	3	4	5	6	7	8	9	**As Bad As You Can Imagine** 10
Your **skin itching** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **skin and/or joint tightening** at their WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth sensitivity** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **genital discomfort** at its WORST? (Women – vagina, vulva, or labia) (Men – penis)	O	O	O	O	O	O	O	O	O	O	O

Eyes	What is your main complaint with regard to your eyes?	
	Please rate how severe this symptom is, from 0 (not at all severe) to 10 (most severe):	0 1 2 3 4 5 6 7 8 9 10

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?
1= mild
2=moderate
3=severe

2. Please circle the number indicating how severe your chronic graft versus host disease symptoms are, where 0 is cGvHD symptoms that are not at all severe and 10 is the most severe chronic GvHD symptoms possible.

0 1 2 3 4 5 6 7 8 9 10

cGvHD symptoms not at all severe — Most severe cGvHD symptoms possible

3. Compared to a month ago, overall would you say that your cGvHD symptoms are:

+3= Very much better
+2= Moderately better
+1=A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

Appendix G: Staging of cGVHD (NIH Criteria)

SARAH CANNON Development Innovations

BMT29

Subject #:_____
Cycle #/Day#:_____
Date:_____

APPENDIX. STAGING OF CHRONIC GVHD (NIH CRITERIA)

The definitions for mild, moderate, and severe chronic GVHD are as follows:
NIH Global Severity of Chronic GVHD
Mild Chronic GVHD
• 1 or 2 organs involved with no more than score 1 *plus*
• Lung score 0

Moderate Chronic GVHD
• 3 or more organs involved with no more than score 1

OR
• At least 1 organ or site with a max score of 2

OR
• Lung score 1

Severe Chronic GVHD
• At least 1 organ with a score of 3

OR
• Lung score of 2 or 3

Key points:
• In skin: higher of the 2 scores to be used for calculating global severity.
• In lung: FEV11 is used instead of clinical score for calculating global severity.
• If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
• If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes), the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

1 The FEV1 is the volume exhaled during the first second of a forced expiratory maneuver started from the level of total lung capacity.
Staging of chronic GVHD as described by Jagasia et al (2015) should be performed using scoring criteria as described below.

Staging of Chronic GVHD (Jagasia et al 2015)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Organ scoring of chronic GVHD. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; LPS, Lansky performance status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *Weight loss within 3 months. †Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. To be completed by specialist or trained medical providers. **Lung scoring should be performed using both the symptoms and FEV_1 scores whenever possible. FEV_1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV_1 scores.

Staging of Chronic GVHD (Continued)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS** **Symptom score**:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **%** FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Organ scoring of chronic GVHD. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; LPS, Lansky performance status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *Weight loss within 3 months. †Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. To be completed by specialist or trained medical providers. **Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

Staging of Chronic GVHD (Continued)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GENITAL TRACT (*See Supplemental figure*[‡]) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs[‡] and females with or without discomfort on exam	☐ Moderate signs[‡] and may have symptoms with discomfort on exam	☐ Severe signs[‡] with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)*	❑ **No GVHD**	❑ **Mild**	❑ **Moderate**	❑ **Severe**

Organ scoring of chronic GVHD. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; LPS, Lansky performance status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *Weight loss within 3 months. †Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. To be completed by specialist or trained medical providers. **Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

Appendix H Response Assessment for cGVHD (NIH Criteria)

SARAH CANNON
Development Innovations

Protocol: BMT29

Cycle#: _____
Patient ID: _____
Date: _____

cGVHD Activity Assessment (Day 1 of Cycles 2 through 7; and then every odd-numbered cycle thereafter starting on Day 1 of Cycle 9, as well as the EOT visit))

Organ	Check if Organ Involved at BL		Score		Response				
			Baseline	Current	Complete Response	Partial Response	Progression	Unchanged	Non-Evaluable
Esophagus	☐	(NIH Esophagus Score)							
Upper GI	☐	(NIH Upper GI Score)							
Lower GI	☐	(NIH Lower GI Score)							
Lungs	☐	(NIH Lung Sx Score)							
		(FEV1%)							
Eyes	☐	(NIH Eye Score)							
Joints & Fascia	☐	(NIH Joint & Fascia Score)							
		(P-ROM Shoulder)							
		(P-ROM Elbow)							
		(P-ROM Wrist/Finger)							
		(P-ROM Ankle)							
Skin	☐	(NIH Skin Score)							
Mouth	☐	(NIH Modified OMRS)							
Liver	☐	(Bilirubin, mg/dL)							
		(ALT, U/L)							
		(ALP, U/L)							
Global	N/A	(Global Severity Rating)							

Overall Response	Complete Response	Partial Response	Lack of Response (Unchanged)	Lack of Response (Mixed)	Lack of Response (Progression)
	☐	☐	☐	☐	☐

Response Assessment for cGVHD (NIH Criteria, continued)

SARAH CANNON
Development Innovations

Protocol: BMT29

Cycle#: _____
Patient ID: _____
Date: _____

Response determination for cGVHD by organ at postbaseline assessment (comparison versus baseline)

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 × ULN
Lungs	• Normal %FEV1 after previous involvement • If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	• Increase by 10% predicted absolute value of %FEV1 • If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	• Decrease by 10% predicted absolute value of %FEV1 • If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale

Response will be assessed using NIH 2014 criteria (Lee et al 2015)

cGVHD Response Definitions

Response	Definition
Complete Response (CR)	Resolution of all manifestations of cGVHD in each organ or site
Partial Response (PR)	Improvement in at least one organ or site without progression in any other organ or site
Lack of Response	
Mixed (LR-M)	Complete or partial response in at least one organ accompanied by progression in another organ
Unchanged (LR-U)	Outcomes that do not meet the criteria for complete response, partial response, progression or mixed response
Progression (LR-P)	Progression in at least one organ or site without a response in any other organ or site

Investigator Signature _____

Date: _____

Appendix I Lee cGVHD Symptom Score

SARAH CANNON Development Innovations

BMT29 **Cycle#:_____** **Patient ID: _____**

By circling one number per line, please indicate how much you have been bothered by the following problems in the past 7 days:

Skin		Not at all	Slightly	Moderately	Quite a bit	Extremely
1.	Abnormal skin color	0	1	2	3	4
2.	Rashes	0	1	2	3	4
3.	Thickened skin	0	1	2	3	4
4.	Sores on skin	0	1	2	3	4
5.	Itchy skin	0	1	2	3	4
Eyes and Mouth		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
6.	Dry eyes	0	1	2	3	4
7.	Need to use eye drops frequently	0	1	2	3	4
8.	Difficulty seeing clearly	0	1	2	3	4
9.	Need to avoid certain foods due to mouth pain	0	1	2	3	4
10.	Ulcers in mouth	0	1	2	3	4
11.	Receiving nutrition from and intravenous line or feeding tube	0	1	2	3	4
Breathing		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
12.	Frequent cough	0	1	2	3	4
13.	Colored sputum	0	1	2	3	4
14.	Shortness of breath with exercise	0	1	2	3	4
15.	Shortness of breath at rest	0	1	2	3	4
16.	Need to use oxygen	0	1	2	3	4
Eating and Digestion		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
17.	Difficulty swallowing solid foods	0	1	2	3	4
18.	Difficulty swallowing liquids	0	1	2	3	4
19.	Vomiting	0	1	2	3	4
20.	Weight loss	0	1	2	3	4
Muscles and Joints		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
21.	Joint and muscle aches	0	1	2	3	4
22.	Limited joint movement	0	1	2	3	4
23.	Muscle cramps	0	1	2	3	4
24.	Weak muscled	0	1	2	3	4
Energy		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
25.	Loss of energy	0	1	2	3	4
26.	Need to sleep more/take naps	0	1	2	3	4
27.	Fevers	0	1	2	3	4
Mental and Emotional		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
28.	Depression	0	1	2	3	4
29.	Anxiety	0	1	2	3	4
30.	Difficulty sleeping	0	1	2	3	4

Patient signature: _____ **Date: _____**

Appendix J: Cytochrome P450 3A4 Inhibitors and Inducers

Source: http://www.mayomedicallaboratories.com/it-mmfiles/Cytochrome_P450_3A4_and_3A5_Known_Drug_Interaction_Chart.pdf

CYP3A4 Inhibitors

Strong Inhibitors
Clarithromycin
Indinavir
Itraconazole
Ketoconazole
Nefazodone
Ritonavir
Saquinavir
Suboxone
Telithromycin

Intermediate Strength Inhibitors
Aprepitant
Erythromycin
Fluconazole
Verapamil
Diltiazem

Weak Inhibitors
cimetidine

Other Possible Inhibitors
Amiodarone
Boceprevir
Chloramphenicol
Ciprofloxacin
Delaviridine
Diethyl-dithiocarbamate
Fluvoxamine
Gestodene
Imatinib
Mibefradil
Mifepristone
Norfloxacin
Norfluoxetine
Starfruit
Telaprevir
Voriconazole

CYP3A4 Inducers
Barbiturates
Carbamazepine
Efavirenz
Glucocorticoids
Modafinil
Nevirapine
Oxcarbazepine
Phenobarbital
Phenytoin
Pioglitazone
Rifabutin
St. John's Wort
Troglitazone