Clinical Study Protocol

INCB 18424-271 / NCT02953678

A Single-Cohort, Phase 2 Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease

Product:	**INCB018424**
IND Number:	**77456**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Date of Protocol:	**14 JUN 2016**
Date of Amendment 1:	**12 SEP 2016**
Date of Amendment 2:	**04 OCT 2016**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 11, 50, 54, 56, and 312 as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-271 Protocol Amendment 2 (dated 04 OCT 2016) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

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(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

SYNOPSIS

Name of Investigational Product: INCB018424

Title of Study: A Single-Cohort, Phase 2 Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease

Protocol Number: INCB 18424-271 | **Study Phase:** 2

Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
Assess the efficacy of ruxolitinib in combination with corticosteroids in subjects with Grade II to IV steroid-refractory acute graft-versus-host disease (GVHD).	Overall response rate (ORR) at Day 28, defined as the proportion of subjects demonstrating a complete response (CR), very good partial response (VGPR), or partial response (PR).
Secondary Objectives	**Secondary Endpoints**
Assess additional response and longer-term efficacy outcomes in the study population.	Key secondary endpoint: Six-month duration of response (DOR), defined as the time from first response until GVHD progression or death. DOR will be assessed when all subjects complete the Day 180 visit.
	ORR, defined as the proportion of subjects demonstrating a CR, VGPR, PR at Days 14, 56, and 100.
	Three-month DOR, defined as the time from first response until GVHD progression or death, when all subjects complete the Day 84 visit.
	Nonrelapse mortality (NRM), defined as the proportion of subjects who died due to causes other than malignancy relapse at Months 6, 9, 12, and 24.
	Relapse rate, defined as the proportion of subjects whose underlying malignancy relapses.
	Relapse-related mortality rate, defined as the proportion of subjects whose malignancy relapses and has a fatal outcome.
	Failure-free survival (FFS), defined as the proportion of subjects who are still alive, have not relapsed, have not required additional therapy for acute GVHD, and have not demonstrated signs or symptoms of chronic GVHD, at Month 6.
	Overall survival (OS), defined as the time from study enrollment to death due to any cause.
Assess the incidence and severity of adverse events (AEs) and serious adverse events (SAEs).	Summaries of clinical safety data (eg, AEs, infections) will be tabulated and listed.
Evaluate the pharmacokinetics of ruxolitinib when administered in combination with corticosteroids.	Maximum observed plasma drug concentration (C_{max}), minimum observed plasma drug concentration (C_{min}), time of maximum observed plasma drug concentration (t_{max}), area under the plasma drug concentration versus time curve (AUC), and apparent clearance of study drug from plasma (CL/F).

[redacted]

Overall Study Design:

This is an open-label, single-cohort, multicenter Phase 2 study of ruxolitinib in combination with corticosteroids for the treatment of steroid-refractory Grades II to IV acute GVHD. Eligible subjects will begin treatment at 5 mg twice daily (BID) ruxolitinib; if hematologic parameters are stable and no treatment-related toxicity is observed after the first 3 days of treatment, the dose may be increased to 10 mg BID. Ruxolitinib may be tapered after Day 180 provided the subject has achieved CR or VGPR and corticosteroids have been discontinued for at least 8 weeks. Corticosteroids will be administered at a starting dose of 2.0 mg/kg per day (unless otherwise indicated) on Day 1 and will be tapered as appropriate. Subjects will receive study treatment until treatment failure (progression of GVHD, no response, or requiring additional systemic therapy), unacceptable toxicity, or death. Continued use of anti-infective medications, GVHD prophylaxis medications (including calcineurin inhibitors), transfusion support, and topical steroid therapy is permitted.

Severity of GVHD will be assessed from screening through end of treatment (EOT) using the Mount Sinai Acute GVHD International Consortium (MAGIC) guidelines. Adverse events and SAEs will be assessed from the time of consent through 30 to 35 days after the EOT as per National Cancer Institute CTCAE v4.03. Subjects will be assessed for efficacy (including overall response, NRM, FFS, DOR, relapse rate, relapse-related mortality rates, and OS), safety (including AEs, SAEs, and clinical/laboratory assessments), [redacted]

Study Population:

Subjects who have developed Grades II to IV steroid-refractory acute GVHD may be eligible candidates for this study.

Key Inclusion Criteria:

- Male or female, 12 years of age or older.
- Have undergone first allogeneic hematopoietic stem cell transplantation (allo-HSCT) from any donor source using bone marrow, peripheral blood stem cells, or cord blood for hematologic malignancies. Recipients of nonmyeloablative and myeloablative conditioning regimens are eligible.

- Clinically suspected Grades II to IV acute GVHD as per MAGIC guidelines, occurring after allogeneic hematopoietic stem cell transplant with any conditioning regimen and any anti-GVHD prophylactic program. Biopsies should be obtained to pathologically confirm acute GVHD; in cases where a biopsy is negative, is unable to be obtained, or is clinically contraindicated, clinical suspicion of acute GVHD by the treating physician is sufficient, provided that alternative diagnoses of drug effects or infection are adequately ruled out.
- Subjects with steroid-refractory acute GVHD, defined as any of the following:
  - Subjects with progressive GVHD (ie, increase in stage in any organ system or any new organ involvement) after 3 days of primary treatment with methylprednisolone $\geq$ 2 mg/kg per day (or equivalent).
  - Subjects with GVHD that has not improved (ie, decrease in stage in at least 1 involved organ system) after 7 days of primary treatment with methylprednisolone $\geq$ 2 mg/kg per day (or equivalent).
  - Subjects who previously began corticosteroid therapy at a lower dose (at least 1 mg/kg per day methylprednisolone) for treatment of skin GVHD or skin GVHD accompanied by upper gastrointestinal (GI) GVHD, but develop new GVHD in another organ system.
  - Subjects who cannot tolerate a corticosteroid taper, that is, begin corticosteroids at 2.0 mg/kg per day, demonstrate response, but progress before a 50% decrease from the initial starting dose of corticosteroids is achieved.
- Evidence of myeloid engraftment (eg, absolute neutrophil count $\geq 0.5 \times 10^9$/L for 3 consecutive days if ablative therapy was previously used). Use of growth factor supplementation is allowed.
- Be willing to avoid pregnancy or fathering children based on 1 of the following criteria:
  - Women of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR $\geq$ 12 months of amenorrhea).
  - Woman of childbearing potential who has a negative serum pregnancy test at screening and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.
  - Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.
- Written informed consent and/or assent from the subject, parent, or guardian.
- Willingness to comply with all study visits and procedures.

Key Exclusion Criteria:

- Has received more than 1 allo-HSCT.
- Has received more than 1 systemic treatment in addition to corticosteroids for acute GVHD.
- Presence of GVHD overlap syndrome as per NIH guidelines.
- Presence of an active uncontrolled infection. An active uncontrolled infection is defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs, or radiographic findings attributable to infection. Persisting fever without signs or symptoms will not be interpreted as an active uncontrolled infection.
- Known human immunodeficiency virus infection.
- Active hepatitis B virus (HBV) or hepatitis C virus infection that requires treatment or at risk for HBV reactivation. At risk for HBV reactivation is defined as hepatitis B surface antigen positive or anti–hepatitis B core antibody positive. Previous test results obtained as part of standard of care before allo-HSCT that confirm a subject is immune and not at risk for reactivation (ie, hepatitis B surface antigen negative, surface antibody positive) may be used for purposes of eligibility and tests do not need to be repeated. Subjects with previous positive serology results must have negative polymerase chain

reaction results. Subjects whose immune status is unknown or uncertain must have results confirming immune status before enrollment.

- Serum creatinine > 2.0 mg/dL or creatinine clearance < 40 mL/min measured or calculated by Cockroft-Gault equation.
- Subjects with evidence of relapsed primary disease, or subjects who have been treated for relapse after the allo-HSCT was performed.
- Unresolved toxicity or complications (other than acute GVHD) due to previous allo-HSCT.
- Any corticosteroid therapy for indications other than GVHD at doses of methylprednisolone or equivalent > 1 mg/kg per day within 7 days of enrollment.
- 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).
  - Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia that requires therapy.
  - Clinically significant respiratory disease that requires mechanical ventilation support or 50% oxygen.
- Currently breast feeding.
- Received Janus kinase (JAK) inhibitor therapy after allo-HSCT for any indication. Treatment with a JAK inhibitor before allo-HSCT is permitted.
- Treatment with any other investigational agent, device, or procedure, within 21 days (or 5 half-lives, whichever is greater) of enrollment. Subjects participating in a GVHD prophylaxis study or conditioning regimen should be discussed with the sponsor's medical monitor before enrollment.
- Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
- Known allergies, hypersensitivity, or intolerance to any of the study medications, excipients, or similar compounds.

Study Drug, Dosage, and Mode of Administration:

Subjects will begin treatment at ruxolitinib 5 mg BID; the dose may be escalated to 10 mg BID after 3 days if hematologic parameters are stable and no treatment-related toxicity is observed. Subjects may have dose reductions during the course of treatment based on safety and laboratory assessments. The dose of ruxolitinib may be re-escalated if toxicity management thresholds are met or if a subject experiences a GVHD flare and has adequate hematologic parameters. The dose of ruxolitinib may not exceed 10 mg BID. Tapering of ruxolitinib is permitted provided the subject has reached the Day 180 visit, achieved a CR or VGPR, and discontinued corticosteroid therapy for at least 8 weeks.

Reference Therapy, Dosage, and Mode of Administration:

Subjects will begin treatment at prednisone 2.5 mg/kg per day orally (PO) or methylprednisolone 2.0 mg/kg per day intravenously (IV). Subjects who previously began corticosteroid therapy at a different dose may remain on that dose if considered appropriate by the treating physician. Corticosteroids should be tapered as per institutional guidelines at a rate that is commensurate with resolution of GVHD manifestations.

If GVHD flares during the taper of corticosteroids, then 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 unresponsive to increased corticosteroids, or if multiple flares are observed, then the subject will be considered to have experienced treatment failure.

Study Schedule/Key Study Procedures:

Assessment	Frequency
Consent, medical/disease history	Screening
GVHD biopsy (as appropriate)	Screening
Pregnancy testing (as appropriate)	Screening and as indicated through EOT
Electrocardiogram	Screening and as indicated through EOT
Physical exam/vitals/ECOG	Screening; weekly to Day 56, then every 28 days through EOT; Day 100; safety follow-up
Hematology/chemistry panel	Screening; weekly to Day 56, then every 28 days through EOT; Day 100; safety follow-up
Acute GVHD staging	Screening; weekly to Day 56, then every 28 days through EOT; Days 100, 180, and 365; safety follow-up
[redacted]	[redacted]
Chimerism assessment	Screening, as indicated up to EOT
PTLD assessment	As indicated up to EOT
Steroid dose monitoring	Day 1 through EOT
Concomitant/prophylactic/supportive care medications	Screening through 30 days after EOT
AEs	Screening through 30 days after EOT

PTLD = post-treatment lymphoproliferative disorder.

Acute GVHD Staging and Grading, MAGIC Guidelines

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper GI	Lower GI (Stool Output/Day)
0	No active (erythematous) GVHD rash	< 2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: < 500mL/day or < 3 episodes/day. Child: < 10mL/kg per day or < 4 episodes/day.
1	Maculopapular rash < 25% BSA	2-3 mg/dL	Persistent nausea, vomiting, or anorexia	Adult: 500-999 mL/day or 3-4 episodes/day. Child: 10-19.9 mL/kg per day or 4-6 episodes/day.
2	Maculopapular rash 25%-50% BSA	3.1-6 mg/dL	–	Adult: 1000-1500 mL/day or 5-7 episodes/day. Child: 20-30 mL/kg per day or 7-10 episodes/day.
3	Maculopapular rash > 50% BSA	6.1-15 mg/dL	–	Adult: > 1500 mL/day or > 7 episodes/day. Child: > 30 mL/kg per day or > 10 episodes/day.
4	Generalized erythroderma (> 50%) with bullae	> 15 mg/dL	–	Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume).

BSA = body surface area.
Overall clinical grade (based on most severe target organ involvement):
Grade 0: No Stage 1-4 of any organ.
Grade I: Stage 1-2 skin without liver, upper GI, or lower GI involvement.
Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
Grade III: Stage 2-3 liver and/or Stage 2-3 lower GI, with Stage 0-3 skin and/or Stage 0-1 upper GI.
Grade IV: Stage 4 skin, liver, or lower GI involvement, with Stage 0-1 upper GI.

Estimated Duration of Participation: Subject participation is expected to average 12 months, which includes the following:

- A screening period lasting up to 28 days.
- A treatment period lasting as long as the subject is deriving benefit (estimated 9 months).
- A safety follow-up period lasting 30 to 35 days after treatment ends.
- A survival follow-up period lasting until death, withdrawal of consent, or the end of the study, whichever occurs first.

Estimated Number of Subjects: 70

Estimated Number of Study Sites: 40

Principal Coordinating Investigator: TBD

Statistical Methods:

Approximately 70 subjects are planned for the final analysis of the primary endpoint. A treatment regimen for steroid-refractory GVHD demonstrating an absolute improvement of 20% versus historic data would be considered clinically meaningful. With the assumed true rate of 60%, a sample size of 70 subjects would provide > 90% probability to have a 95% confidence interval with lower limit of ≥ 40%. An interim analysis will be performed for futility once 35 subjects complete the Day 28 visit; if the lower boundary is crossed, the study will be terminated.

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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this clinical study Protocol.

Abbreviation	Definition
AE	adverse event
aGVHD	acute graft-versus-host disease
AIHA	autoimmune hemolytic anemia
allo-HSCT	allogeneic hematopoietic stem cell transplantation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATG	antithymocyte globulin
BID	twice daily
BM	bone marrow
BOOP	bronchiolitis obliterans-organizing pneumonia
BSA	body surface area
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CFR	Code of Federal Regulations
CMV	cytomegalovirus
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
ECG	electrocardiogram
ECP	extracorporeal photopheresis
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
FFS	failure-free survival
GCP	Good Clinical Practice
GFP	green fluorescent protein
GI	gastrointestinal

Abbreviation	Definition
GVH	graft versus host
GVHD	graft-versus-host disease
GVT	graft versus tumor
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IFN-γ	interferon-γ
IFN-γR	interferon-γ receptor
IL	interleukin
IL-2R	interleukin 2 receptor
IN	Investigator Notification
IRB	institutional review board
ITP	idiopathic thrombocytopenic purpura
IUD	intrauterine devices
IUS	intrauterine hormone-releasing system
IV	intravenously
IVRS	interactive voice response system
JAK	Janus kinase
MAGIC	Mount Sinai Acute GVHD International Consortium
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility
MMF	mycophenolate mofetil
MPN	myeloproliferative neoplasm
NCI	National Cancer Institute
NIH	National Institutes of Health
NK	natural killer
NR	no response
NRM	nonrelapse mortality
ORR	overall response rate
OS	overall survival
PBS	phosphate buffered saline

Abbreviation	Definition
PFT	pulmonary function test
PK	pharmacokinetic
PO	orally
PR	partial response
PTLD	post-transplant lymphoproliferative disorder
QD	once daily
RA	rheumatoid arthritis
Retro	retrospective
RNA	ribonucleic acid
SAE	serious adverse event
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TPO	thrombopoietin
Treg	regulatory T cell
ULN	upper limit of normal
VGPR	very good partial response

1. INTRODUCTION

1.1. Overview of Acute Graft-Versus-Host Disease

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective immunotherapy for human cancer (Appelbaum 2007). More than 20,000 allo-HSCTs are performed each year worldwide, primarily for the treatment of hematologic malignancies (Pavletic and Fowler 2012). Acute graft-versus-host disease (GVHD) and chronic GVHD remain major contributors to transplantation-related deaths and the most significant barrier to successful allo-HSCT. Graft-versus-host disease occurs when immune cells transplanted from a nonidentical donor (the graft) recognize the transplant recipient (the host) as foreign, thereby initiating an immune reaction that causes disease in the transplant recipient. Despite prophylactic treatments with immunosuppressive agents, approximately 50% of transplantation recipients develop GVHD. Most graft-versus-host (GVH) reactions are undesirable and affect multiple organs; however, GVH reactions against hematopoietic tissue targets are desirable and critical for the cure of hematologic malignancies (ie, the graft-versus-tumor [GVT] effect) and for donor immune-hematopoietic system engraftment. These disparate effects of GVH reactions are difficult to separate, and any strategies directed against GVHD may adversely affect survival by increasing malignancy relapse, graft rejection, and the frequency and severity of infections (Pavletic and Fowler 2012).

There are few therapeutic studies for acute GVHD, and currently no agents are approved by the FDA for either prevention or treatment of acute GVHD (Martin et al 2009). In response to this limitation, an NIH-FDA public workshop was convened in 2009 to facilitate clinical development programs for products to prevent or treat acute GVHD. A major topic of this workshop was defining the optimal endpoint and timing for evaluating new therapeutics for acute GVHD. Although universally accepted as a suitable endpoint for regulatory approval in oncology clinical studies, survival is not always a practical endpoint for developing GVHD therapeutics, owing to the multiple contributing causes of death in the allogeneic transplantation setting (Martin 2008).

Treatment options for GVHD, including modulation of donor-alloreactive effector T-cells, remain a major focus of current therapies for acute GVHD. Other cell populations, including regulatory T cells (Tregs), dendritic cells, natural killer (NK) T cells, and B cells, or other mechanisms, such as modulation of tissue or vascular endothelium damage signals, may also represent targets for GVHD therapy. At diagnosis, the extent of individual organ involvement and overall grade of acute GVHD should be documented, taking into account all organ involvement, as this has prognostic significance. Acute GVHD diagnosis should be confirmed by biopsy of an affected organ if possible; in addition, other non-GVHD complications involving the skin, liver, and gastrointestinal (GI) tract should be ruled out. Although diagnostic biopsies are highly specific if current histopathology criteria are used, the sensitivity of these biopsies is only approximately 60%; therefore, the ultimate acute GVHD diagnosis and decision to treat systemically is based on careful integration of all available clinical information (Weisdorf et al 2003).

The classic target organs for acute GVHD are the skin (severity ranging from maculopapular rash to erythroderma and bullae formation), the GI tract (resulting in nausea, vomiting, abdominal cramps, or diarrhea), and the liver (resulting in hyperbilirubinemia, jaundice, or elevated transaminases). The hematopoietic system can also be targeted, resulting in complete donor lymphohematopoietic chimerism and the GVT response against hematologic malignancies. Endothelium, lungs, and other organs can also be targeted, although skin, gut, and liver involvement are the only organs scored in the current grading system.

The severity of acute GVHD is graded according to the degree of involvement of the skin, liver, and GI tract. Two of the more commonly used grading systems are the Glucksberg system (I-IV) and the International Bone Marrow Transplant Research system (A-D; Glucksberg et al 1974, Rowlings et al 1997). These grading systems have evolved over time, which included refinement of the Glucksberg system by an NIH working group to include persistent nausea with histologic evidence of GVHD as Stage 1 upper GI acute GVHD (Przepiorka et al 1995). The NIH criteria have been further refined by the Mount Sinai Acute GVHD Consortium (MAGIC) to standardize the collection of complex clinical data from multiple organ systems in multicenter studies (Harris et al 2016).

Two subcategories have been recognized within the broader category of acute GVHD: 1) classic acute GVHD (eg, maculopapular erythematous rash, GI symptoms, cholestatic hepatitis), occurring within 100 days after transplantation or donor leukocyte infusion and 2) persistent, recurrent, or late acute GVHD, occurring beyond 100 days after transplantation or donor leukocyte infusion. Both acute GVHD subentities occur without the presence of diagnostic or distinctive chronic GVHD manifestations (Pavletic 2012). The current NIH consensus criteria for assessment of chronic GVHD suggest that clinical manifestations rather than time after transplantation should determine whether the clinical GVHD syndrome is considered acute or chronic (Jagasia et al 2015). Some signs and symptoms are common to both acute GVHD and chronic GVHD (eg, erythema, maculopapular rash, nausea, vomiting or diarrhea, and elevated liver function tests) and thus other characteristics must be used to distinguish between the 2 categories.

1.1.1. First-Line Treatment of Acute GVHD

Corticosteroids are used as conventional first-line systemic therapy, and response rates between 50% and 60% have been previously reported (Saliba et al 2012, MacMillan et al 2010, Levine et al 2010). Treatment with methylprednisone at 2 mg/kg per day (or an oral prednisone equivalent) has been long accepted as standard first-line therapy for acute GVHD in the United States (Martin et al 2012) and Europe (Ruutu et al 2014). In standard-risk cases of upper GI GVHD, reduced doses of systemic corticosteroids (eg, 1 mg/kg per day) and topical steroids have been shown to be equally effective (Mielcarek et al 2009). Neither response rate nor overall survival (OS) advantages were observed in acute GVHD patients treated with corticosteroids at doses higher than 2.5 mg/kg per day (Van Lint et al 1998).

Because only approximately 50% of acute GVHD patients respond to systemic steroids and many of these responses are not durable, attempts have been made to evaluate other agents in addition to prednisone compared with prednisone alone for initial therapy, such as antibodies against interleukin 2 receptor (IL-2R), high-dose steroids, horse antithymocyte globulin, anti–tumor necrosis factor drugs, mycophenolate mofetil, pentostatin, and sirolimus (Figure 1;

Cahn et al 1995, Lee et al 2004, Cragg et al 2000, Couriel et al 2009, Levine et al 2008, Alousi et al 2009, Pidala et al 2009). In most cases, the second agent yielded modest benefit; however, a study of daclizumab found the additional intervention to be detrimental (Figure 1).

Figure 1: Summary of Studies Evaluating Agents for Initial Therapy of Acute GVHD[a]

Reference	Agent	Phase	No. of Patients	Response Assessment	CR Proportion	CR or PR Proportion	6-Month Survival
Comparative studies							
[7]	High-dose pred	3	48				0.74
	Pred		47				0.63
[8]	Low-dose pred	Retro	347				0.77
	Pred		386				0.69
[9]	Pred short taper	3	14				0.86
	Pred long taper		16				0.81
[10]	Basiliximab pred	3	35	Day 20	0.54	0.63	0.78
	Pred		34	Day 20	0.44	0.71	0.66
[12]	Horse ATG pred	3	50	Day 42		**0.27**[c]	**0.48**
	Pred		46	Day 42		0.55	0.65
[11][b]	Daclizumab pred	3	53	Day 42	0.43	0.51	0.53[c]
	Pred		49	Day 42	0.49	0.53	0.76
[13][b]	Etanercept pred	2	61	Day 28	**0.69**[c]		0.69
	Pred	Retro	99	Day 28	0.33		0.55
[14][b]	Infliximab pred	3	29	Day 28	0.55		0.52
	Pred		28	Day 28	0.54		0.54
Single-arm studies							
[17]	MMF pred	Pilot	17			0.65	0.80
[18][b]	Etanercept pred	2	46	Day 28	**0.26**	0.48	0.56
[18][b]	MMF pred	2	45	Day 28	0.60	0.78	0.71
[18][b]	Denileukin pred	2	47	Day 28	0.53	0.60	0.58
[18][b]	Pentostatin pred	2	42	Day 28	0.38	0.62	0.56
[19]	Sirolimus	Pilot	10	Best	0.50		
Results with prednisone							
[15]	Pred	3	114	Day 28	0.25	0.59	0.73
[16]	Pred	Retro	864	Day 28	0.53	0.65	0.65

aGVHD indicates acute graft-versus-host disease; CR, complete response; PR, partial response; pred, prednisone; Retro, retrospective; ATG, antithymocyte globulin; MMF, mycophenolate mofetil.

[a]Nonsteroid treatment results that fall outside the 95% confidence interval for the aggregated overall average of all studies are shown in bold. See Figures 1, 2, and 3.

[b]Rationale for planned sample size and corresponding power estimates are reported.

[c]Statistically significant difference compared to controls, as reported by the study authors.

Source: Martin et al 2012.

1.1.2. Treatment for Steroid-Refractory Acute GVHD

If acute GVHD progresses within 3 days or does not improve after 5 to 7 days of initial treatment, it is considered to be steroid refractory, and second-line therapy is warranted (Pavletic and Fowler 2012). There are no FDA-approved agents for steroid-refractory acute GVHD; numerous combination approaches have been studied, but data do not support the recommendation or exclusion of any particular regimen. Very few prospective studies have evaluated second-line therapy for acute GVHD (Figure 2; Martin et al 2012), and interpretation of these studies is hampered by heterogeneity of subject population, small sample sizes, and lack of standardization in the study design (including timing of the response, different response criteria, and absence of validated endpoints). In addition, treatment of steroid-refractory acute GVHD is associated with significant toxicities, high failure rates, and 6-month survival rate of 49%. Agents that have been investigated over the last 2 decades in these studies include low-dose methotrexate, mycophenolate mofetil, extracorporeal photopheresis, IL-2R targeting (ie, basiliximab, daclizumab, denileukin, and diftitox), alemtuzumab, horse antithymocyte globulin, etanercept, infliximab, and sirolimus (Martin et al 2012).

Figure 2: Summary of Studies Evaluating Agents for Second-Line Therapy of Acute GVHD[a]

Agent	Phase	No. of Patients	Response Assessment	CR Proportion	CR or PR Proportion	6-Month Survival
Methotrexate	Retro	12	Day 28[b]	0.42	0.58	0.58
MMF	Retro	13	Best	0.15	0.46	0.66
MMF	Retro	10	Best	0	0.60	0.77
MMF	Retro	48	Best	0.31	**0.79**	0.47
MMF	Retro	27	Best	0.26		0.52
ECP	Retro	33	Best[b]	**0.55**	0.76	**0.76**
ECP	Retro	23	Best[b]	0.48	0.48	0.57
Basiliximab	2	23	Day 7[b]	0.17	0.83	0.55
Daclizumab	2	43	Day 43	0.37	0.51	
Daclizumab	2	12	Day 28[b]	0.08	0.50	0.33
Daclizumab	Retro	57	Day 43	0.33	0.54	**0.28**
Inolimomab	2	14	Best[b]	0.14	0.43	0.36
Denileukin diftitox	1	32	Best	0.38	0.53	
Denileukin diftitox	2	22	Best	0.18	**0.27**	
Alemtuzumab	2	18	Day 28[b]	0.33	0.83	0.71
Alemtuzumab	2	10	Best[b]	0.20	0.50	**0**
Alemtuzumab	Retro	18	Day 56[b]	0.28	0.62	0.61
Horse ATG	Retro	22	Day 28		**0.18**	
Horse ATG	Retro	58	Day 21[b]	**0.07**	**0.28**	**0.17**
Horse ATG	Retro	79	Day 28	0.20	0.54	0.44
Horse ATG	2/3	47	Best[b]	0.32	0.57	0.45
Horse ATG	3	27	Best[b]	0.33	0.56	0.55
Etanercept	Retro	13	Day 56	0.38	0.46	0.77
Infliximab	Retro	21	Day 7[b]	**0.62**	0.67	0.52
Horse ATG + etanercept	Retro	16	Best[b]	**0.69**	0.81	0.56
Dacliz + etanercept	2	21	Best[b]	0.38	0.67	0.57
Dacliz + infliximab	Retro	22	Day 42[b]	0.45	0.82	**0.86**
Dacliz/inflix/horse ATG	Retro	12	Best[b]	**1.00**	**1.00**	0.73
Sirolimus	Retro	34	Best	0.44	0.76	0.48

aGVHD = acute graft-versus-host disease; ATG = antithymocyte globulin; CR = complete response; ECP = extracorporeal photopheresis; MMF = mycophenolate mofetil; PR = partial response; Retro = retrospective.

[a] Treatment results that fall outside the 95% confidence interval (CI) for the aggregated overall average of all studies are shown in bold.

[b] The report did not indicate whether absence of further systemic treatment was a criterion for response. In all other reports, subjects who had further systemic treatment were classified as not having a CR or PR.

Source: Martin et al 2012.

Given these data, the choice of a second-line regimen is made based on the outcome of prior treatments, desired toxicity profile, considerations for drug interactions, logistical practicality, costs, and subject and physician preferences. Second-line treatments, especially those associated with suppression of T cells, are associated with increased infection and viral reactivation (including cytomegalovirus [CMV], Epstein-Barr virus, human herpes virus 6, adenovirus, and polyoma).

1.2. Ruxolitinib Background

1.2.1. Pharmacology

Ruxolitinib is a novel, potent and selective inhibitor of the Janus kinases (JAKs) with selectivity for JAK1 and JAK2 (Quintás-Cardama et al 2010). Ruxolitinib potently inhibits JAK1 and JAK2 (IC_{50} < 5 nM), yet it does not significantly inhibit a broad panel of 28 kinases (< 30% inhibition) when tested at 200 nM (approximately 100 × the average IC_{50} value for JAK1 and JAK2 enzyme inhibition). In cell-based assays relevant to the pathogenesis of myeloproliferative neoplasms (MPNs), such as JAK/signal transducers and activators of

transcription (STAT) signaling and the growth of cytokine-dependent tumor cell lines, ruxolitinib demonstrates IC_{50} values of 80 to 300 nM. This effect is not due to general cytotoxicity, because ruxolitinib (up to 25 μM) had no significant effect on the growth of a cytokine-independent, Breakpoint cluster region-Abelson–driven cell line. In addition, ruxolitinib inhibited JAK/STAT signaling and growth of a cell line expressing the constitutively active JAK2 mutant (JAK2V617F) that has been implicated in the pathogenesis of the majority of Philadelphia chromosome negative MPNs. Ruxolitinib was also tested in cell-based assays relevant to the increased inflammatory cytokine levels observed in MPNs that contribute to MPN-related systemic symptoms. Ruxolitinib potently inhibited interleukin (IL)-23–stimulated IL-22 production in human T cells (IC_{50} = 50 nM), as well as IL-6, granulocyte-macrophage colony–stimulating factor and thrombopoietin (TPO)-induced STAT3 phosphorylation in human peripheral blood mononuclear cells with IC_{50} values < 100 nM. Ruxolitinib also inhibited granulocyte colony-stimulating factor–stimulated STAT3 phosphorylation in human neutrophils (IC_{50} = 28 ± 9 nM), as well as TPO-induced STAT3 phosphorylation in human whole blood (IC_{50} = 281 ± 62 nM). Finally, ruxolitinib inhibited the production of IL-17 in response to IL-23 in T cells and the production of monocyte chemotactic protein-1 in response to IL-6 in peripheral blood mononuclear cells with IC_{50} values of ≤ 120 nM (Fridman et al 2011).

Ruxolitinib inhibited splenomegaly in mice resulting from intravenous (IV) inoculation of cells expressing the clinically relevant JAK2V617F mutation (Quintás-Cardama et al 2010). After 3 weeks of treatment, more than 90% of vehicle-treated mice had succumbed to disease while more than 90% of ruxolitinib-treated mice survived. Treatment with ruxolitinib also reduced inflammatory cytokine levels in these mice. The effects of ruxolitinib were also tested in a mouse disease model of polycythemia vera–like disease, based on transplantation of a 1:1 ratio of JAK2 wild-type green fluorescent protein (GFP)–expressing murine bone marrow cells with JAK2V617F-positive murine bone marrow cells, which have a repopulation advantage. In this model, oral ruxolitinib treatment at doses of 30 or 90 mg/kg twice daily (BID) for 21 consecutive days reduced levels of phosphorylated STAT5 (pSTAT5) in the spleen, as well as the spleen size. Ruxolitinib also effectively reduced the red cell parameters (red blood cell count, hemoglobulin, hematocrit, and reticulocyte count) and neutrophil count. The treatment was well-tolerated as assessed by monitoring body weight, and histological assessments of spleen and bone marrow samples post-therapy revealed a decrease of hypercellularity (erythroid and myeloid lineages) in ruxolitinib-treated groups as compared with vehicle-treated animals. However, no significant decrease in the mutant allele burden surrogate readout (percentage of GFP-negative cells, ie, cells expressing JAK2V617F) was observed, as assessed by flow cytometry. Treatment of mice with ruxolitinib in a cytokine-dependent multiple myeloma xenograft model resulted in a dose-dependent suppression of phosphorylated STAT3 and tumor growth. Efficacy was also observed in additional preclinical tumor models representing both hematologic and solid tumors. Taken together, these data indicate that ruxolitinib will be able to inhibit wild-type and mutant JAKs in the clinical setting and are consistent with its observed efficacy in patients with MPNs.

1.2.2. Clinical Studies

As of 22 FEB 2016, more than 8350 patients have received ruxolitinib in company-sponsored studies. In addition, more than 70 interventional or observational studies sponsored by third

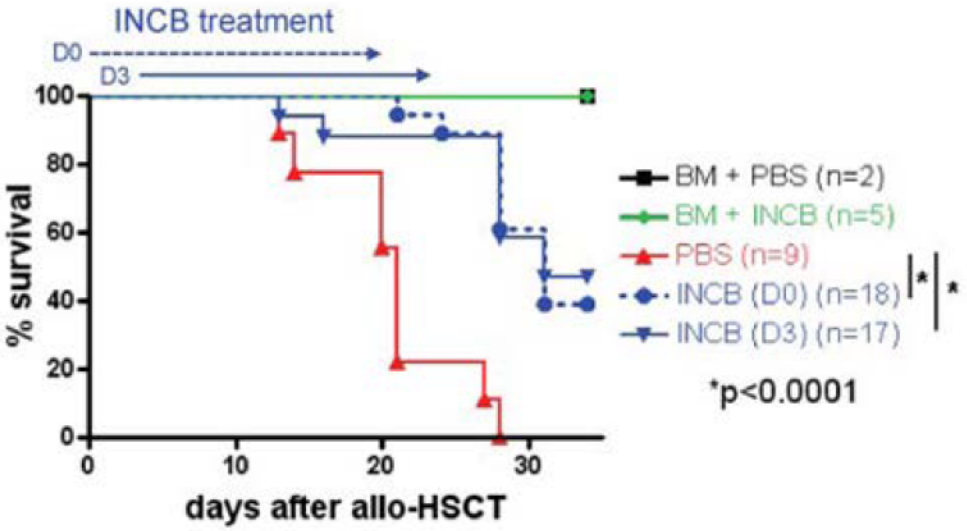
parties are ongoing or completed. Additional details regarding the study designs and primary endpoints of these studies are summarized in the ruxolitinib Investigator's Brochure (IB).

1.3. Study Rationale

1.3.1. Animal Studies in Acute GVHD Models

To determine the role of JAK/STAT signaling in GVHD, major histocompatibility (MHC)-mismatched allo-HSCT was performed in mice [B6 (H-2^b) to Balb/c(H-2^d)]. In this model, interferon γ receptor (IFN-γR) signaling was shown to play a major role in T-cell trafficking to GVHD target organs via CXCR3. Mice transplanted with IFN-γR -/- T cells had improved survival and less clinical GVHD compared with mice transplanted with wild-type T cells. Furthermore, pharmacologic inhibition of interferon signaling with a JAK/STAT signaling inhibitor, ruxolitinib, for 20 days resulted in the decreased expression of CXCR3, reduced GVHD, and improved survival after allo-HSCT in mice (Figure 3; Choi et al 2012).

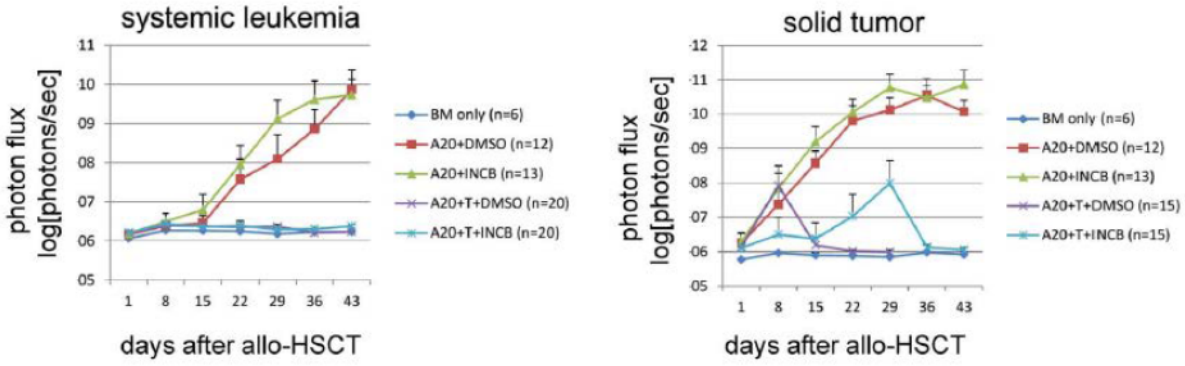
Figure 3: Effect of Ruxolitinib on Survival in Mice After Allo-HSCT



BM = bone marrow; INCB = ruxolitinib (INCB018424); PBS = phosphate buffered saline.
Source: Choi et al 2012.

This effect was shown to be mediated by altered trafficking of T cells to GVHD target organs. The pharmacologic blockade of JAK/STAT signaling in wild-type T-cells using the JAK/STAT-signaling inhibitor, ruxolitinib, resulted in a similar effect to IFN-γR-/- T cells both *in vitro* (reduction of CXCR3 expression in T cells) and *in vivo* (mitigation of GVHD after allo-HSCT). Ruxolitinib also reduced GVHD and preserved the beneficial GVT effect in 2 different mouse MHC-mismatched allo-HSCT models and 2 different mouse leukemia models (lymphoid leukemia and myeloid leukemia; Figure 4; Choi et al 2014). This result was due to an alteration in T-cell trafficking without affecting T-cell expansion. In addition, prolonged administration of ruxolitinib further improved survival after allo-HSCT. These data suggest that pharmacologic inhibition of JAK/STAT signaling might be a promising therapeutic approach to achieve the beneficial antileukemia effect and overcome human leukocyte antigen barriers in allo-HSCT.

Figure 4: Ruxolitinib Maintains a Beneficial GVT Effect as Determined by Bioluminescence Imaging in the A20 Leukemia Model



BM = bone marrow; INCB = ruxolitinib (INCB018424).
Source: Choi et al 2014.

In a separate study, *in vivo* JAK/STAT signaling inhibition improved survival of mice developing acute GVHD and reduced histopathological GVHD grading, serum levels of proinflammatory cytokines, and expansion of alloreactive luc-transgenic T cells (Choi et al 2012).

It was shown that the JAK1/2 inhibitor ruxolitinib impaired differentiation of $CD4^+$ T cells into interferon γ (IFN-γ) and IL-17A–producing cells and that both T-cell phenotypes are linked to GVHD. Additionally, ruxolitinib treatment in allo-HSCT recipients increased $FoxP3^+$ Tregs, which are linked to immunologic tolerance.

1.3.2. Clinical Experience With JAK Inhibitors for the Treatment of Acute GVHD

Clinical experience with ruxolitinib in patients with steroid-refractory GVHD was initially reported in 6 patients based on a prospective protocol (Spoerl et al 2014). Results were updated in a retrospective analysis of 95 patients with steroid-refractory acute GVHD (n = 54, all Grade III or IV) or steroid-refractory chronic GVHD (n = 41, all moderate or severe) who were treated with ruxolitinib at a dose of 5 to 10 mg BID (Zeiser et al 2015). Of the 45 patients with acute GVHD (all of whom with Grades 3 or 4 disease), an overall response rate (ORR) of 81.5% was reported, including 25 CRs (46.3%). The median time to response was 1.5 weeks (range 1-11) after initiation of ruxolitinib therapy. In addition, a 6-month survival estimate of 79% (67.3%-90.7%, 95% CI) was reported, with a median follow-up time of 26.5 weeks. Graft-versus-host disease relapses were reported in 6.8% (3/44) of patients. A significant decline in levels of IL-6 and soluble IL-2 receptor were observed in 12 of 25 evaluable patients treated at one center. Cytomegalovirus reactivation was observed in 33.3% (18/54) acute GVHD patients and was controlled using antiviral therapy while ruxolitinib treatment continued. Cytopenias were also observed during treatment with ruxolitinib in 55.5% (30/54) patients; however, cytopenias were reported before treatment with ruxolitinib in 51.7% (28/54). Malignancy relapse was reported in 9.3% (5/54).

A Phase 1 clinical study evaluating INCB039110, a potent, selective inhibitor of JAK1, is currently underway.

Overall, these results suggest that inhibition of JAK/STAT signaling is a promising mechanism in the treatment of acute and chronic GVHD. New treatments for the therapy of acute GVHD after allo-HSCT are urgently needed. Novel treatments with agents targeting the JAK-STAT pathway appear to decrease acute GVHD while preserving GVT in murine models by targeting the IFN-γ pathway in activated T cells responsible for acute GVHD. The preclinical data with clinical proof-of-principle findings with ruxolitinib provides a strong rationale and justification of further investigating ruxolitinib with standard corticosteroid doses as a treatment option for patients with acute GVHD.

This study will include subjects who are 12 years and older as data from a Phase 1 study in pediatric subjects showed that safety of ruxolitinib was generally favorable and pharmacokinetic (PK) data were comparable to that in adults (Loh et al 2015). Adolescents between the ages of 12 and 18 years comprise approximately 5% of the adult aGVHD population, and standard treatment does not differ between adolescents and adults.

1.3.3. Rationale for Chosen Endpoints

As previously described, very few prospective studies have evaluated second-line therapy for GVHD, and interpretation of these studies is hampered by heterogeneity of patient population and lack of standardization in the study design, including timing of the response, absence of validated evaluation of endpoints, and small numbers of patients. Response rates range between 18% to 79%, and treatment of steroid-refractory acute GVHD is associated with significant toxicities, high failure rates, and 6-month survival rate of 49% (Martin et al 2012).

In order to assess whether response is a significant predictor to long-term clinical benefit, Saliba et al (2012) reported Day 28 response as an independent and strongest predictor statistically of nonrelapse mortality (NRM) at 6 months and at 24 months. Patients with a CR or PR by Day 28 after initiation of systemic therapy had a significantly lower 6-month cumulative incidence of NRM (16%) than patients whose acute GVHD did not respond to therapy by Day 28 (48%, $P = 0.005$). The impact of Day 28 response on 6-month NRM was independent of acute GVHD severity. Levine et al (2008) reported similar findings showing Day 28 response being predictive of NRM and survival at 6 and 9 months. These findings were further supported by MacMillan et al (2012) in a retrospective study of 864 patients that reported Day 28 and 56 responses were similarly effective in predicting 2-year NRM.

1.4. Potential Risks and Benefits of the Treatment Regimen

The primary clinical risks with ruxolitinib treatment are the potential sequelae of decreased hematopoietic proliferation attributable to the inhibition of growth factor pathways associated with JAK inhibition. Dose-dependent, reversible thrombocytopenia, anemia, and neutropenia were the most frequent treatment-emergent adverse events (TEAEs) observed during the Phase 3 clinical studies of ruxolitinib in patients with myelofibrosis. Increased rates of infection and anemia are potential risks of myelosuppression. In healthy volunteers, rheumatoid arthritis patients, and patients with pancreatic cancer or hormone-refractory prostate cancer, the effects on hematopoietic proliferation are less pronounced, presumably because of greater bone marrow reserve. The most frequent nonhematologic adverse events (AEs) were mild, reversible increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), bruising,

hypercholesterolemia, dizziness, headache, and urinary tract infections. For a comprehensive assessment of the risks of ruxolitinib, refer to the IB.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	**Primary Endpoint**
Assess the efficacy of ruxolitinib in combination with corticosteroids in subjects with Grades II to IV steroid-refractory acute GVHD.	ORR at Day 28, defined as the proportion of subjects demonstrating a CR, very good partial response (VGPR), or PR.
Secondary Objectives	**Secondary Endpoints**
Assess additional response and longer-term efficacy outcomes in the study population.	Key secondary endpoint: Six-month duration of response (DOR), defined as the time from first response until GVHD progression or death. DOR will be assessed when all subjects complete the Day 180 visit.
	ORR, defined as the proportion of subjects demonstrating a CR, VGPR, or PR at Days 14, 56, and 100.
	Three-month DOR, defined as the time from first response until GVHD progression or death, when all subjects complete the Day 84 visit.
	NRM, defined as the proportion of subjects who died due to causes other than malignancy relapse at Months 6, 9, 12, and 24.
	Relapse rate, defined as the proportion of subjects whose underlying malignancy relapses.
	Relapse-related mortality rate, defined as the proportion of subjects whose malignancy relapses and has a fatal outcome.
	Failure-free survival (FFS), defined as the proportion of subjects who are still alive, have not relapsed, have not required additional therapy for acute GVHD, and have not demonstrated signs or symptoms of chronic GVHD, at Month 6.
	OS, defined as the time from study enrollment to death due to any cause.
Assess the incidence and severity of AEs and serious adverse events (SAEs).	Summaries of clinical safety data (eg, AEs, infections) will be tabulated and listed.
Evaluate the PK of ruxolitinib when administered in combination with corticosteroids.	Maximum observed plasma drug concentration (C_{max}), minimum observed plasma drug concentration (C_{min}), time of maximum observed plasma drug concentration (t_{max}), area under the plasma drug concentration versus time curve (AUC), and apparent clearance of study drug from plasma (CL/F).

3. SUBJECT ELIGIBILITY

Deviations from eligibility criteria are not allowed, because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the Protocol is essential.

3.1. Subject Inclusion Criteria

A subject who meets all of the following criteria may be included in the study:

1. Male or female, 12 years of age or older.
2. Has undergone first allo-HSCT from any donor source (matched unrelated donor, sibling, haploidentical) using bone marrow, peripheral blood stem cells, or cord blood for hematologic malignancies. Recipients of nonmyeloablative and myeloablative transplants are eligible.
3. Clinically suspected Grades II to IV acute GVHD as per MAGIC guidelines, occurring after allo-HSCT with any conditioning regimen and any anti-GVHD prophylactic program. Biopsies should be obtained to pathologically confirm acute GVHD; in cases where a biopsy is negative, is unable to be obtained, or is clinically contraindicated, clinical suspicion of acute GVHD by the treating physician is sufficient, provided that alternative diagnoses of drug effects or infection are adequately ruled out.
4. Subjects with steroid-refractory acute GVHD, defined as any of the following:
    a. Subjects with progressive GVHD (ie, increase in stage in any organ system or any new organ involvement) after 3 days of primary treatment with methylprednisolone $\geq$ 2 mg/kg per day (or equivalent).

b. Subjects with GVHD that has not improved (ie, decrease in stage in at least 1 involved organ system) after 7 days of primary treatment with methylprednisolone ≥ 2 mg/kg per day (or equivalent).
c. Subjects who previously began corticosteroid therapy at a lower dose (at least 1 mg/kg methylprednisolone) for treatment of skin GVHD or skin GVHD accompanied by upper GI GVHD, but develop new GVHD in another organ system.
d. Subjects who cannot tolerate a corticosteroid taper, that is, begin corticosteroids at 2.0 mg/kg per day, demonstrate response, but progress before a 50% decrease from the initial starting dose of corticosteroids is achieved.

5. Evidence of myeloid engraftment (eg, absolute neutrophil count [ANC] $\geq 0.5 \times 10^9$/L for 3 consecutive days if ablative therapy was previously used). Use of growth factor supplementation is allowed.
6. Be willing to avoid pregnancy or fathering children based on 1 of the following criteria:
   a. Women of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea).
   b. Woman of childbearing potential who has a negative serum pregnancy test at screening and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
   c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
7. Written informed consent and/or assent from the subject, parent or guardian.
8. Willingness to comply with all study visits and procedures.

3.2. Subject Exclusion Criteria

1. Has received more than 1 allo-HSCT.
2. Has received more than 1 systemic treatment in addition to corticosteroids for acute GVHD.
3. Presence of GVHD overlap syndrome as per NIH guidelines (Jagasia et al 2015).
4. Subjects who have had a splenectomy.
5. Presence of an active uncontrolled infection. An active uncontrolled infection is defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs, or radiographic findings attributable to infection. Persisting fever without signs or symptoms will not be interpreted as an active uncontrolled infection.
6. Known human immunodeficiency virus infection.

7. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection that requires treatment or at risk for HBV reactivation. At risk for HBV reactivation is defined as hepatitis B surface antigen positive or anti–hepatitis B core antibody positive. Previous test results obtained as part of standard of care before allo-HSCT that confirm a subject is immune and not at risk for reactivation (ie, hepatitis B surface antigen negative, surface antibody positive) may be used for purposes of eligibility, and tests do not need to be repeated. Subjects with previous positive serology results must have negative polymerase chain reaction results. Subjects whose immune status is unknown or uncertain must have results confirming immune status before enrollment.
8. Serum creatinine > 2.0 mg/dL or creatinine clearance < 40 mL/min as measured or calculated by Cockroft-Gault equation.
9. Subjects with evidence of relapsed primary disease, or subjects who have been treated for relapse after the allo-HSCT was performed.
10. Unresolved toxicity or complications (other than acute GVHD) due to previous allo-HSCT.
11. Any corticosteroid therapy for indications other than GVHD at doses of methylprednisolone or equivalent > 1 mg/kg per day within 7 days of enrollment.
12. Severe organ dysfunction unrelated to underlying GVHD, including:
    a. Cholestatic disorders or unresolved veno-occlusive disease of the liver (defined as persistent bilirubin abnormalities not attributable to GVHD and ongoing organ dysfunction).
    b. Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia that requires therapy.
    c. Clinically significant respiratory disease that requires mechanical ventilation support or 50% oxygen.
13. Currently breast feeding.
14. Received JAK inhibitor therapy after allo-HSCT for any indication. Treatment with a JAK inhibitor before allo-HSCT is permitted.
15. Treatment with any other investigational agent, device, or procedure, within 21 days (or 5 half-lives, whichever is greater) of enrollment. Subjects participating in a GVHD prophylaxis study or conditioning regimen should be discussed with the sponsor's medical monitor before enrollment.
16. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
17. Known allergies, hypersensitivity, or intolerance to any of the study medications, excipients, or similar compounds.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an open-label, single-cohort, multicenter Phase 2 study of ruxolitinib in combination with corticosteroids for the treatment of steroid-refractory Grades II to IV acute GVHD. Eligible subjects will begin treatment at ruxolitinib 5 mg BID; if hematologic parameters are stable and no treatment-related toxicity is observed after the first 3 days of treatment, the dose may be increased to 10 mg BID. Ruxolitinib may be tapered after Day 180 provided the subject has achieved a CR or VGPR and corticosteroids have been discontinued for at least 8 weeks. Subjects who are still receiving calcineurin inhibitors or other agents for GVHD prophylaxis at this time may continue to do so at the treating investigator's discretion. Corticosteroids will be administered at a starting dose of 2.0 mg/kg per day (unless otherwise indicated) on Day 1 and will be tapered as appropriate. Subjects will receive study treatment until treatment failure (progression of GVHD, no response, or requiring additional systemic therapy), unacceptable toxicity, or death. Continued use of anti-infective medications, GVHD prophylaxis medications (including calcineurin inhibitors), transfusion support, and topical steroid therapy is permitted.

Severity of GVHD will be assessed from screening through end of treatment (EOT) using the Mount Sinai Acute GVHD International Consortium (MAGIC) guidelines. Adverse events and SAEs will be assessed from the time of consent through 30 to 35 days after the EOT as per National Cancer Institute (NCI) CTCAE v4.03. Subjects will be assessed for efficacy (including overall response, NRM, FFS, DOR, relapse rate, relapse-related mortality rates, and OS), safety (including AEs, SAEs, and clinical/laboratory assessments), [redacted]

4.2. Measures Taken to Avoid Bias

Acute GVHD response and AEs will be assessed using standardized objective criteria (MAGIC guidelines [Appendix B] and NCI CTCAE v4.03 [2009], respectively).

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

This study will enroll approximately 70 subjects with steroid-refractory acute GVHD from approximately 40 study sites.

4.3.2. Replacement of Subjects

Not applicable.

4.4. Duration of Treatment and Subject Participation

After signing the informed consent form (ICF), screening assessments may be completed over a period of up to 28 days. Each subject enrolled in the study may continue to receive study treatment for as long as benefit is observed and/or treatment withdrawal criteria are not met. If

the subject discontinues study treatment (ie, ruxolitinib and corticosteroids), then the treatment period will end, and the subject will enter the follow-up period (see Section 6.4). The safety follow-up period will last 30 to 35 days, and the survival follow-up period will last until death, withdrawal of consent, or the end of the study, whichever occurs first. Study participation is expected to average approximately 12 months per individual subject.

4.5. Overall Study Duration

The study begins when the first subject signs the informed consent. Subjects who are still receiving study treatment at the time of the primary analysis will be permitted to continue on study treatment until treatment withdrawal criteria are met (Section 5.5). All subjects will be followed for survival until death, withdrawal of consent, or the end of the study, whichever occurs first. The study will end and the final analysis will occur once 75% of subjects have achieved 2-year NRM, died or are lost to follow-up, whichever occurs first.

4.6. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the institutional review board (IRB)/independent ethics committee (IEC) in writing of the study's completion or early termination, and send a copy of the notification to the sponsor or sponsor's designee and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively or if required by regulatory decision. If the study is terminated prematurely, then the sponsor will notify the investigators, the IRBs and IECs, and the regulatory bodies of the decision and reason for termination of the study.

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Each subject will be identified in the study by a subject ID number, which is a combination of the site ID and subject number. Site staff should contact the interactive voice response system (IVRS) to obtain the subject ID number during screening.

Site staff will contact the IVRS to enroll the subject and obtain the initial study drug assignment. The investigator or designee will select the assigned bottles of study drug from their stock that correspond to the number provided by the IVRS, record the bottle numbers in the electronic case report form (eCRF), and dispense the study drug to the subject. All subsequent dispensing of study drug should follow this process. Full details will be provided in the IVRS manual.

All subject numbers will be 6 digits; the first 3 digits will be the site number, and the last 3 digits will be the subject's number. This subject number will be maintained throughout the study and will not be reassigned. Subjects who withdraw consent or discontinue from the study after being assigned a subject number will retain their initial number.

For subjects who signed an ICF but are not allocated and for subjects who are allocated but were not treated, refer to the eCRF Completion Guidelines for instruction on which eCRFs to complete.

5.1.2. Randomization

Not applicable.

5.2. Study Drugs

5.2.1. Ruxolitinib

5.2.1.1. Description and Administration

Ruxolitinib 5 mg tablets are round and white to off-white in color.

Subjects will begin treatment at ruxolitinib 5 mg BID; if hematologic parameters are stable and no treatment-related toxicity is observed after the first 3 days of treatment, the dose may be increased to 10 mg BID. Stable hematologic parameters are defined as the absence of a $\geq$ 50% decrease in platelet counts and/or ANC relative to Day 1. Ruxolitinib may be taken without regard to food except on days when PK samples are drawn; on those days, subjects should be instructed to fast and refrain from taking ruxolitinib until PK samples are collected. See Section 7.7.1 for additional information.

Subjects may have dose reductions or modifications of ruxolitinib during the course of treatment based on AEs, clinical evaluation, and laboratory assessments. See Section 5.4.1 for dose modifications of ruxolitinib.

Subjects are permitted to remain on ruxolitinib treatment until withdrawal from study treatment is considered necessary as per Section 5.5.

5.2.1.2. Supply, Packaging, and Labeling

Ruxolitinib will be supplied as 5 mg tablets packaged in 60-count high-density polyethylene bottles. All tablet excipients comply with the requirements of the applicable compendial monographs.

All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country and will state "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

5.2.1.3. Storage

Bottles of ruxolitinib tablets should be stored at room temperature, 15°C to 30°C (59°F to 86°F).

5.2.1.4. Instruction to Subjects for Handling Ruxolitinib

The subject must be instructed in the handling of study drug as follows:

- To store the study drug at room temperature.
- To only remove from the study drug bottle/kit the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- To report any missed doses.
- To take study drug within 1 hour after completing a meal (morning and evening meal) with a glass of water.
- Not to take another dose if vomiting occurs after taking study drug.
- To keep study drug in a safe place and out of reach of children.
- To bring all used and unused study drug kits to the site at each visit.

5.2.2. Corticosteroids

Either oral prednisone or IV methylprednisolone may be used to begin corticosteroid treatment at the investigator's discretion.

5.2.2.1. Prednisone

5.2.2.1.1. Description

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 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg tablets.

5.2.2.1.2. Supply, Packaging, and Labeling

Investigators are responsible for ensuring that subjects receive commercially available supplies of prednisone for the duration of the study treatment period. Incyte may provide prednisone where required by applicable law or regulation.

5.2.2.1.3. Storage

Prednisone tablets should be stored in accordance with local prescribing information requirements.

5.2.2.2. Methylprednisolone

5.2.2.2.1. Description

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; it is insoluble in chloroform and is very slightly soluble in acetone.

5.2.2.2.2. Supply, Packaging, and Labeling

Investigators are responsible for ensuring that subjects receive commercially available supplies of methylprednisolone for the duration of the study treatment period. Incyte may provide methylprednisolone where required by applicable law or regulation.

5.2.2.2.3. Storage

Methylprednisolone (unreconstituted product or solution) should be stored in accordance with local prescribing information.

5.2.2.3. Administration of Corticosteroids

Subjects will receive prednisone 2.5 mg/kg per day orally (PO) or methylprednisolone 2.0 mg/kg per day IV. Subjects who previously began corticosteroid therapy at a different dose may remain on that dose if considered appropriate by the treating physician. Corticosteroids should be tapered as per institutional guidelines at a rate that is commensurate with resolution of GVHD manifestations.

A recommended tapering schedule is provided in Table 1.

Table 1: Recommended Corticosteroid Administration Table, Days 1 Through 28

Study Days	Dose
Days 1-5	Prednisone 2.5 mg/kg QD PO (or methylprednisolone 2.0 mg/kg per day IV)
Days 6-10	Prednisone 2.0 mg/kg QD PO (or methylprednisolone 1.6 mg/kg per day IV)
Days 11-15	Prednisone 1.5 mg/kg QD PO (or methylprednisolone 1.2 mg/kg per day IV)
Days 16-20	Prednisone 1.0 mg/kg QD PO (or methylprednisolone 0.8 mg/kg per day IV)
Days 21-25	Prednisone 0.5 mg/kg QD PO (or methylprednisolone 0.4 mg/kg per day IV)
Days 26-28	Prednisone 0.25 mg/kg QD PO (or methylprednisolone 0.2 mg/kg per day IV)

QD = once daily.

If GVHD flares during the taper of corticosteroids, then 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 unresponsive to increased corticosteroids, or if multiple flares are observed, then the subject will be considered to have experienced treatment failure.

Corticosteroids may be taken or administered without regard to food except on days when PK samples are drawn; on those days, subjects should be instructed to fast and refrain from taking corticosteroids until after PK samples are collected. See Section 7.7.1 for additional information.

5.2.2.4. Prophylactic and Supportive Care 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.

Systemic and topical GVHD prophylaxis medications (eg, cyclosporine, methotrexate, tacrolimus) may be continued at therapeutic doses as appropriate based on stage and sites of disease.

Additional supportive care measures (eg, use of antimotility agents for diarrhea management) are permitted at the investigator's discretion.

5.3. Treatment Compliance

Compliance with all study-related medications should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with ruxolitinib will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Subjects will be instructed to bring all study-related medications with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

Although commercial supplies of corticosteroids will be used, dose changes and interruptions will also be documented in the medical record and monitored by the sponsor or its designee. As corticosteroid dose strengths and administration types will vary, compliance with corticosteroids will not be calculated.

5.4. Treatment Interruptions and Adjustments

5.4.1. Dose Modifications

Dose interruptions and modifications may occur for individual study subjects based on the presence or absence of toxicity.

5.4.2. Criteria and Procedures for Dose Interruptions and Adjustments of Ruxolitinib

5.4.2.1. Dose Interruptions and Reductions

5.4.2.1.1. Toxicity Management

Treatment with ruxolitinib may be delayed up to 14 days to allow for resolution of toxicity (Table 2). Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The investigator should contact the sponsor medical monitor to discuss cases where treatment has been delayed for more than 14 days before restarting treatment.

Because subjects may enter the study with compromised bone marrow function, these dose reductions are provided as guidelines; individual decisions regarding dose reduction should be made using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study drug and the subject'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.

Subjects who are currently receiving ruxolitinib 10 mg BID may be reduced to 5 mg BID; subjects receiving 5 mg BID may be reduced further to 5 mg QD. Subjects who are unable to tolerate ruxolitinib at a dose of 5 mg QD should be withdrawn from study treatment (Table 3).

Table 2: Guidelines for Interruption and Restarting of Ruxolitinib

ADVERSE EVENT	ACTION TAKEN
Chemistry	
• AST and/or ALT > 3.0 × ULN in subjects with normal ALT/AST at baseline.	**Step 1:** Interrupt study treatment up to 14 days until the toxicity has resolved to ≤ Grade 1. Exceptions require sponsor approval. **Step 2:** Restart study treatment at same dose. If assessed as related to study treatment, restart study treatment at next lower dose and monitor as clinically indicated. **NOTE:** In subjects with GVHD-related chemistry elevations at baseline, contact the sponsor medical monitor to discuss clinical management and possible dose reductions.
• Total bilirubin elevations that occur in the presence of GVHD response that, in the investigator's opinion, cannot be attributed to new liver GVHD or concomitant therapy.	• Total bilirubin 3.0–5.0 × ULN: – **Repeat** assessment within 7 days. If elevation persists: ▪ **Reduce** ruxolitinib dose by 1 level until bilirubin ≤ 1.5 × ULN. ▪ **Resume** previous dose if resolved in 14 days; if > 14 days, maintain reduced dose. • Total bilirubin >5.0–10.0 × ULN: – Repeat assessment within 7 days. If elevation persists: ▪ **Hold** ruxolitinib until bilirubin ≤ 1.5 × ULN. ▪ **Monitor** LFTs weekly or more frequently as appropriate. ▪ **Resume** previous dose if resolved in 14 days; if > 14 days, resume at reduced dose. • Total bilirubin > 10.0 × ULN: – **Repeat** assessment within 7 days. If elevation persists: ▪ **Hold** ruxolitinib until bilirubin ≤ 1.5 × ULN. ▪ **Resume** at reduced dose if resolved in 14 days; if > 14 days, discontinue ruxolitinib and monitor as appropriate.
• Total bilirubin elevations that occur in subjects with Stage 1/2 liver GVHD that, in the investigator's opinion, cannot be attributed to worsening liver GVHD or concomitant therapy.	• Total bilirubin > 3.0 × ULN: – **Repeat** assessment within 7 days. If elevation persists: ▪ **Reduce** ruxolitinib dose by 1 dose level. • If bilirubin ≤ 3.0 × ULN, may **resume** previous dose.

Table 2: Guidelines for Interruption and Restarting of Ruxolitinib (Continued)

ADVERSE EVENT	ACTION TAKEN
Hematology	
• ANC $< 1.0 \times 10^9$/L, suspected as unrelated to study treatment (eg, GVHD, active CMV viremia).	**Step 1:** Reduce dose of ruxolitinib by 1 dose level. **Step 2:** Monitor ANC count as clinically indicated. **Step 3:** If ANC count is $\geq 1.0 \times 10^9$/L for more than 7 days, then the previous dose of ruxolitinib may be resumed.
• ANC $< 1.0 \times 10^9$/L, suspected as related to study treatment. • ANC $< 1.0 \times 10^9$/L, with an oral temperature of at least 38.5°C OR with ≥ Grade 3 infection. • ANC $< 0.5 \times 10^9$/L.	**Step 1:** Interrupt study treatment for up to 14 days. **Step 2:** Monitor ANC count as clinically indicated. **Step 3:** If ANC count is $\geq 1.0 \times 10^9$/L for more than 7 days, then ruxolitinib may be restarted at 1 dose level below the current dose. **Step 4:** If ANC count is $\geq 1.0 \times 10^9$/L for more than 7 days after treatment at a reduced dose, the previous dose level of ruxolitinib may be resumed.
• Platelet count is $< 10 \times 10^9$/L, or platelet count has decreased by ≥ 50% from baseline, suspected as unrelated to study treatment.	**Step 1:** Reduce dose of ruxolitinib by 1 dose level. **Step 2:** Monitor platelet count as clinically indicated. **Step 3:** If platelet count returns to 20×10^9/L for more than 7 days, then ruxolitinib may be restarted at 1 dose level below the current dose.
• Platelet count is $< 10 \times 10^9$/L, or platelet count has decreased by ≥ 50% from baseline, suspected as related to study treatment. • Platelets $< 20 \times 10^9$/L, with an oral temperature of at least 38.5°C.	**Step 1:** Interrupt study treatment for up to 14 days. **Step 2:** Monitor platelet count as clinically indicated. **Step 3a:** If platelet count returns to 20×10^9/L for more than 14 days, then the dose of ruxolitinib may be resumed. **Step 3b:** If platelet count does not return to $< 10 \times 10^9$/L and there is no platelet transfusion-independent recovery to above $< 10 \times 10^9$/L, then a bone marrow biopsy should be performed. If megakaryocytic hypoplasia and no platelet transfusion-independent recovery are observed within 72 hours, then study treatment should be discontinued. **Step 4:** If platelet count remains $\geq 20 \times 10^9$/L for more than 7 days after treatment at a reduced dose, then the previous dose level of ruxolitinib may be resumed.
Other toxicities	
• Any Grade 1 or Grade 2 toxicity.	Continue treatment and treat the toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care.	**Step 1:** Interrupt study treatment up to 14 days until toxicity resolves to ≤ Grade 1. **Step 2:** Restart study treatment at same dose; if assessed as related to study treatment, then restart study treatment at next lower dose, and monitor as clinically indicated.
• Any recurrent Grade 3 toxicity at 5 mg QD dose.	Discontinue study treatment; follow-up per Protocol. Exceptions require sponsor approval.
• Any other Grade 4 toxicity.	Discontinue study treatment; follow-up per Protocol.

ULN = upper limit of normal.

Table 3: Dose Reduction Levels for Ruxolitinib

Current Dose	First Dose Reduction	Second Dose Reduction
10 mg BID	5 mg BID	5 mg QD
5 mg BID	5 mg QD	Discontinue

5.4.2.1.2. Coadministration With Strong CYP3A4 Inhibitors or Dual CYP2C9/CYP3A4 Inhibitors

Ruxolitinib is mainly eliminated in humans by oxidative metabolism catalyzed predominantly by cytochrome P450 (CYP) 3A4 and CYP2C9 and is not a substrate for transporters including P-glycoprotein (P-gp). Therefore, concomitant medications that inhibit CYP3A4 and CYP2C9 enzymes might increase exposure to ruxolitinib. See Section 5.6 for additional details.

5.4.2.2. Dose Escalation of Ruxolitinib

Subjects will begin treatment at ruxolitinib 5 mg BID; if hematologic parameters are stable and no treatment-related toxicity is observed after the first 3 days of treatment, the dose may be increased to 10 mg BID. Stable hematologic parameters are defined as the absence of a $\geq$ 50% decrease in platelet counts and/or ANC relative to Day 1.

As described in Table 2, subjects who have had a dose reduction of ruxolitinib in order to manage toxicity may resume treatment at the previous dose if hematologic parameters meet the required threshold(s).

Subjects who have previously had a reduction in the dose of ruxolitinib may have their dose re-escalated if a GVHD flare is experienced, provided that hematologic thresholds are described in Table 2 are met. Dose re-escalation levels of ruxolitinib are described in Table 4.

Dose increases may not exceed 10 mg BID.

Table 4: Dose Escalation Levels for Ruxolitinib

Current Dose	First Dose Escalation	Second Dose Escalation
5 mg QD	5 mg BID	10 mg BID
5 mg BID	10 mg BID	–

5.4.2.3. Tapering of Ruxolitinib

If a subject has achieved CR or VGPR at Day 180, investigators may begin to taper the dose of ruxolitinib by 1 dose level provided corticosteroids have been discontinued for at least 8 weeks following institutional guidelines. Subjects who are still receiving calcineurin inhibitors or other agents for GVHD prophylaxis at this time may continue to do so at the treating investigator's discretion. In addition, subjects must not be experiencing any Grade 2 or higher hematologic toxicity related to ruxolitinib or symptoms of an active infection. Subsequent reductions to the dose of ruxolitinib may occur after an additional 56 days have elapsed provided the aforementioned requirements are still being met.

Investigators wishing to initiate a taper of ruxolitinib at an earlier timepoint may do so upon consultation with and approval from the sponsor's medical monitor.

If GVHD signs/symptoms worsen during the taper of ruxolitinib, the dose may be escalated by 1 dose level as indicated in Table 4; if the subject requires additional systemic therapy (includes restarting of corticosteroids), then the subject would be considered as having progression of disease and would be withdrawn from study treatment.

If subjects completely taper off ruxolitinib and GVHD signs/symptoms reappear at a later time, ruxolitinib therapy may be restarted at the treating investigator's discretion, and the subject would resume the assessment schedule using the original Day 1 as a reference point.

5.4.3. Criteria and Procedures for Dose Interruptions or Adjustments of Corticosteroids

Corticosteroid doses should be tapered as per the recommended tapering schedule in Table 1 or as per institutional guidelines; further dose modifications may be made at the treating investigator's discretion.

5.4.4. Criteria for Permanent Discontinuation of Study Treatment

The occurrence of an unacceptable toxicity not caused by the underlying disease will be presumed to be related to study drug treatment and will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- Persistent AE requiring a delay of therapy for more than 14 days, unless a greater delay has been approved by the sponsor.

5.5. Withdrawal of Subjects From Study Treatment

The decision to discontinue study treatment will not constitute study completion (see Section 5.5.3). In the event that the decision is made to discontinue study treatment, the treatment period will be considered complete, and the follow-up period will begin.

5.5.1. Withdrawal Criteria

Subjects **must** be withdrawn from study treatment for the following reasons:

- The subject has experienced an unacceptable toxicity.
- Relapse of the underlying malignancy.
- The subject is unable to tolerate ruxolitinib at a dose of 5 mg QD.
- Additional systemic therapy is required for GVHD progression or lack of response, including corticosteroids equal to or greater than the dose used on Study Day 1.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The subject becomes pregnant.

- Consent is withdrawn.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A subject **may** be withdrawn from study treatment as follows:

- If, during the course of the study, a subject is found not to have met eligibility criteria, then the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study.
- If a subject is noncompliant with study procedures or study drug administration in the investigator's opinion, then the sponsor should be consulted for instruction on handling the subject.

5.5.2. Withdrawal Procedures

In the event that the decision is made to permanently discontinue the study drug, the subject will be withdrawn from the study, and the EOT visit should be conducted. Reasonable efforts should be made to have the subject return for a follow-up visit. These visits are described in Section 6. The last date of the last dose of study drug and the reason for subject withdrawal will be recorded in the eCRF.

If a subject is withdrawn from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF.
- The EOT visit should be performed.
- The date of the EOT visit should be registered in the IVRS.
- Subjects must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the subject discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, subjects will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments.

5.5.3. Study Completion

A subject will be considered as completing the study if they meet any of the following criteria:

- Subject dies and a date of death is available.
- Subject is known to have died; however, the date of death cannot be obtained. (NOTE: Every effort must be made to obtain the date of death.)
- Subject has discontinued study treatment and has withdrawn consent for collection of follow-up anticancer and survival data.

5.6. Concomitant Medications

5.6.1. Permitted Medications

Concomitant treatments and/or procedures that are required to manage a subject's medical condition (including prophylactic and/or supportive care medications as described in Section 5.2.2.4) during the study will also be recorded in the eCRF.

5.6.2. Restricted Medications

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

- Aspirin in doses exceeding 125 mg per day is not permitted. Low-dose aspirin (≤ 125 mg per day) is permitted unless clinically contraindicated.
- Coadministration with strong CYP 3A inhibitors; consider alternative agents with less CYP3A inhibition (Appendix C). Differences in individual sensitivity and variation CYP enzyme inhibition may result in the need for dose reduction of ruxolitinib and/or corticosteroids as appropriate. The sponsor medical monitor may be consulted for advice when using these agents.
- Coadministration with CYP3A4 inducers (Appendix C).
- If concomitant administration of an anticoagulant/antiplatelet medication is indicated, then caution and enhanced monitoring is required. History of thrombocytopenia should be a factor in the choice of anticoagulant and dose.

5.6.3. Prohibited Medications

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

- Any concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, or tumor embolization). Use of biologic agents for treatment of noncancer indications is permitted.
- Any secondary GVHD therapy due to insufficient response/progression on study treatment.
- Concomitant use of a JAK inhibitor.
- Initiating therapy with an investigational medication unless otherwise approved by the medical monitor.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments (see Table 5), and all laboratory assessments will be performed as indicated in Table 6. Table 7 presents a summary of clinical laboratory analytes to be assessed. The order of assessments is suggested by the order of mention within the schedule. See Section 7 for instructions on each assessment. Further details of study procedures and assessments can be found in the study reference manual.

Table 5: Schedule of Assessments

Item	Section	Screening Phase	Treatment Phase[a]													EOT	Follow-Up Phase	
		-28 to -1	D1	D3	D7	D14	D21	D28	D35	D42	D49	D56[b]	D100	D180	D365[c]		Safety[d]	Survival
Informed consent	7.1	X																
Inclusion/exclusion criteria	3	X																
Contact IVRS	7.2	X	X					X				X	X		X	X		X
Demography/disease history	7.3	X																
Prior/concomitant medications	7.4	X	X													X	X	
Supportive care medications	5.2.2.4	X	X													X	X	
AE assessment	7.5.1	X	X													X	X	
Physical examination	7.5.2	X	X		X	X	X	X	X	X	X	X	X		X	X	X	
Vital signs	7.5.3	X	X		X	X	X	X	X	X	X	X	X		X	X	X	
ECOG performance status	7.5.4	X	X		X	X	X	X	X	X	X	X	X		X	X	X	
12-lead ECG	7.5.5	X	As indicated													X		
Acute GVHD grading and response assessment	7.6.1	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]																		
Chimerism assessment	7.6.3	X	As indicated															
PTLD assessment	7.6.4		As indicated															
Dispense study drug	5.1		X					X				X			X			
Study drug compliance	5.3		X					X				X			X	X		
Steroid dose monitoring	5.3		X													X		
Survival follow-up	6.4																	X[e]

ECG = electrocardiogram; PTLD = post-transplant lymphoproliferative disorder.
[a] A ± 2-day window is permitted to facilitate scheduling during the treatment phase.
[b] After Day 56, visits will occur every 28 days and will include all Day 56 assessments.
[c] The Day 365 visit will also serve as the regularly scheduled visit occurring every 28 days after Day 56 (ie, Day 364).
[d] Thirty to 35 days after EOT. For subjects withdrawing due to reasons other than GVHD progression, GVHD status should be assessed every 28 days.
[e] Every 8 weeks ± 7 days.

Table 6: Laboratory Assessments

Item	Section	Screening Phase	Treatment Phase[a]												EOT	Safety Follow-Up
		-28 to -1	D1[b]	D3	D7	D14	D21	D28	D35	D42	D49	D56[c]	D100	D180	D365[d]	
Chemistry panel	7.5.6.1	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Hematology	7.5.6.2	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Hepatitis screening	7.5.6.4	X															
Serum pregnancy test (childbearing females only)	7.5.6.3	X														X	
Urine pregnancy test[e] (childbearing females only)	7.5.6.3		X														
PK assessment[f]	7.7		X		X	X											
Correlative study blood collection	7.8	X	X		X	X		X				X[g]	X	X	X	X	

[a] A ± 2-day window is permitted to facilitate scheduling during the treatment phase.
[b] Day 1 laboratory assessments do not need to be repeated if screening assessments were performed in preceding 7 days.
[c] After Day 56, visits will occur every 28 days and will include all Day 56 assessments.
[d] The Day 365 visit will also serve as the regularly scheduled visit occurring every 28 days after Day 56 (ie, Day 364).
[e] Urine pregnancy tests are only required if medically indicated and should be confirmed with a serum pregnancy test.
[f] Samples to be collected at predose and at 1 hour ± 15 minutes, at 2 hours ± 30 minutes, and between 4 and 8 hours postdose.
[g] Day 56 only.

Table 7: Clinical Laboratory Analytes

Serum Chemistries	Hematology[a]	Other
Albumin	Hematocrit	Serum pregnancy test
ALP	Hemoglobin	Urine pregnancy test[b]
ALT	Mean corpuscular volume	
AST	Platelet count	
Bicarbonate	Red blood cell count	
Blood urea nitrogen	Reticulocyte count	
Calcium	White blood cell count	
Chloride	White blood cell differential (5 parts):	**Hepatitis Screening Tests**
Creatinine	• Basophils	Hepatitis B surface antigen
Glucose	• Eosinophils	Hepatitis B surface antigen antibody
Lactate dehydrogenase	• Lymphocytes	Hepatitis B core antibody
Phosphorus	• Monocytes	Hepatitis C virus antibody
Potassium	• Neutrophils	HCV-RNA
Sodium		HBV-DNA
Total bilirubin		
Total protein		

ALP = alkaline phosphatase.
[a] Hematology and chemistry assessments will be performed locally.
[b] Urine pregnancy tests are only required if medically indicated.

6.1. Screening

The screening period is the interval between signing the ICF and the day that the subject is enrolled in the study (Day 1). The screening period may not exceed 28 days. Informed consent must be obtained before performing any study-specific procedures that are not considered standard of care. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during this period.

Procedures conducted as part of the subject's routine clinical management (eg, blood count, imaging study) and obtained before signing the ICF may be used for screening or baseline purposes, provided that the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study. Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during the screening period if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before enrollment will be used to determine subject eligibility. Treatment should start as soon as possible, but within 2 days after the date of enrollment. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status (eg, following recovery from an infection).

6.2. Treatment

The treatment period begins on the day that the subject receives the first dose of study drug through the point at which the principal investigator determines that the subject will be permanently discontinued from the study drug. Dates for subsequent study visits will be determined based on this day and should occur within ± 2 days of the scheduled date unless delayed for safety reasons. During the Day 1 visit, results from screening visit evaluations should be reviewed to determine whether the subject continues to meet the eligibility requirements as specified in the Protocol.

6.3. End of Treatment

If a decision is made that the subject will permanently discontinue study treatment, then the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, then the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The subject should be encouraged to return for the follow-up visit.

6.4. Follow-Up

6.4.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 35 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 30 after the last dose of study drug, the date of the follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

6.4.2. GVHD Assessment Follow-Up

Subjects who discontinue study treatment for reasons other than progression of GVHD will move into the disease status follow-up period and should be assessed every 28 days to monitor disease status. Every effort should be made to collect information regarding disease status until one of the following occurs:

- GVHD progression
- Relapse of malignancy
- Death
- End of study

6.4.3. Survival Follow-Up

Once a subject has confirmed GVHD progression or starts a new GVHD therapy, the subject moves into the survival follow-up period and should be contacted by telephone, email, or visit at least every 8 weeks (± 7 days) to assess for new GVHD therapy and survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.5. Unscheduled Visits

Unscheduled visits may be held at any time at the investigator's discretion, and appropriate clinical and laboratory measurements performed based on AEs or other findings.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject before conducting any study-specific procedures using an ICF approved by the local IRB/IEC that contains all elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject. Local and institutional guidelines for ICF content and administration must be followed; the original signed ICF must be retained by the investigator, and a copy of the signed ICF must be provided to the study subject. The informed consent process for each subject must be documented in writing within the subject source documentation. Subjects of childbearing potential must agree to take appropriate measures to avoid pregnancy in order to participate in the study (see Appendix A).

7.2. Interactive Response Technology Procedure

The IVRS will be contacted to obtain a subject ID number when a subject enters the screening phase. Upon determining that the subject is eligible for study entry, the IVRS will be contacted to obtain study drug assignment. Additionally, the IVRS will be contacted every 28 days to update study drug supply. See Section 5.1.1 for additional information.

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

Demographic data and a complete medical and medication history will be collected at screening.

7.3.2. Disease Characteristics and Treatment History

A disease-targeted medical and medication history including hematologic malignancy type, current GVHD staging, date of diagnosis, sites of disease, prior anticancer therapy, ablation therapy, prophylaxis therapy, donor type, and other details related to the disease under study will be collected at screening.

7.4. Prior and Concomitant Medications

Prior and concomitant medications will be reviewed to determine subject eligibility. All concomitant medications and measures must be recorded in the eCRF, and any medication received or procedure performed within 30 days before enrollment and up to the end of study will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are

required to manage a subject's medical condition during the study will also be recorded in the eCRF.

7.5. Safety Assessments

7.5.1. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 8.

7.5.2. Physical Examination

The targeted physical examination will be a symptom-directed evaluation conducted by the investigator or a medically qualified designee. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, body temperature, and body weight. Blood pressure and pulse will be taken with the subject in the recumbent, semirecumbent, or sitting position. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.4. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status (Oken et al 1982; Table 8) will be required at screening and will be assessed at other study visits per Table 5. Performance status must be assessed by a medically qualified individual and recorded in the eCRF.

Table 8: ECOG Performance Status Grades

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

7.5.5. Twelve-Lead Electrocardiograms

A 12-lead ECG will be performed during screening with the subject in a recumbent or semirecumbent position after 5 minutes of rest.

The 12-lead ECG will be interpreted by the investigator at the site and will be used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate.

Electrocardiograms that are identified as abnormal and clinically meaningful compared with the screening assessment should be reported as AEs. For such AEs, the findings of the abnormal ECGs and the corresponding baseline ECG findings must be reported in the eCRF.

An additional ECG will be performed at the EOT visit; additional ECGs may be performed at the investigator's discretion as clinically indicated.

7.5.6. Laboratory Assessments

Blood draws for laboratory assessments will occur at study visits indicated in Table 6. Blood draws will be completed before the subject receives the morning dose of study drug. Specific laboratory assessments are listed in Table 7.

All laboratory assessments will be performed at a local (site) laboratory using institutional best practices. Results and normal reference ranges will be entered into the eCRF.

7.5.6.1. Chemistry

All chemistry assessments will be performed at a local (site) laboratory from blood samples collected using institutional best practices before administration of study drug. Results and normal reference ranges will be entered into the eCRF.

7.5.6.2. Hematology

Hematology assessments, including complete blood count with differential, will be performed at a local (site) laboratory using institutional best practices before administration of study drug. Results and normal reference ranges will be entered into the eCRF.

7.5.6.3. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening and at the EOT visit. Urine pregnancy tests will be conducted only if medically indicated. Urine pregnancy tests will be performed locally. If a urine pregnancy test is positive, then the results should be confirmed with a serum pregnancy test.

If the serum pregnancy test is negative after a urine test was positive, then the investigator will assess the potential benefit/risk to the subject and determine whether it is in the subject's best interest to resume study drug and continue participation in the study.

7.5.6.4. Hepatitis Screening

Subjects with active HBV or HCV infection that requires treatment or who are at risk for HBV reactivation are excluded from the study. At risk for HBV reactivation is defined as hepatitis B surface antigen positive or anti–hepatitis B core antibody positive. Prior test results obtained as part of standard of care before allo-HSCT confirming that a subject is immune and not at risk for reactivation (ie, hepatitis B surface antigen negative, surface antibody positive) may be used for purposes of eligibility, and tests do not need to be repeated. Subjects with prior positive serology results must have negative polymerase chain reaction results. Subjects whose immune status is unknown or uncertain must have results confirming immune status before enrollment as per Table 7.

7.6. Graft-Versus-Host Disease Assessments

7.6.1. Graft-Versus-Host Disease Staging and Grading

Acute GVHD grading will be performed by the investigator on a weekly basis for the first 8 weeks after enrollment, then every 28 days thereafter. Graft-versus-host disease staging and grading will also occur on Days 100, 180, and 365 and at the EOT visit. If subjects withdrew due to reasons other than GVHD progression, then GVHD staging and grading will be assessed at the safety follow-up visit. Data regarding the quantification of aGVHD symptoms (extent of skin rash, total bilirubin level, volume of diarrhea) should be reported using MAGIC guidelines (Harris et al 2016); response will be assessed as per the Center for International Blood and Marrow Transplant Research (CIBMTR) modifications to the IBMTR response index as indicated in Appendix B (CIBMTR 2009, Martin et al 2009).

- Skin:
  - Only areas involved with active erythema should be used for determining body surface area staging based on the rule of nines.
  - A portion of a body area segment may be used for the quantification.
  - Desquamation or fluid-filled bullae should be reported if present as these findings are hallmarks of Stage 4 skin GVHD.
- Liver:
  - Liver GVHD staging is based solely on total (not conjugated/direct) serum bilirubin levels.
  - Liver GVHD manifesting as transaminitis without concomitant elevation in serum bilirubin should be diagnosed when the presence of GVHD is confirmed by liver biopsy (where appropriate) and scored as Stage 0.
  - If bilirubin levels were elevated before the diagnosis of GVHD in another target organ and do not increase further, then liver GVHD should not be diagnosed in the absence of biopsy confirmation. However, if hyperbilirubinemia develops at the same time or after the onset of GVHD in another target organ, then liver GVHD is presumed to be present in the absence of an identified alternative cause.

- Upper GI:
  - Symptoms of concern for upper GI GVHD include anorexia, nausea, vomiting, and dyspepsia, and assessment depends on close attention to caloric intake and symptom reporting.
  - An upper GI endoscopy should be performed whenever possible to confirm upper GI GVHD; however, the diagnosis may be made without biopsy confirmation.
  - Graft-versus-host disease is typically not considered as a possible etiology when nausea lasts fewer than 3 days or with fewer than 2 vomiting episodes per day for at least 2 days or anorexia without weight loss.
- Lower GI:
  - Staging of lower GI GVHD relies on accurate measurement of daily stool volumes and documentation of the presence of hematochezia or severe abdominal pain.
  - In cases when stool volume cannot be closely measured, volume should be calculated based on an average of 200 mL per episode multiplied by the number of episodes in 24-hour period.
  - At the time of GVHD onset, staging should be based on the highest daily volume during the 3 days before diagnosis (excluding volumes attributable to procedures such as bowel preps or endoscopy).
  - After the initiation of treatment, lower GVHD staging should be based on the diarrhea volume using (in the order of preference) the following measurements: 1) average of 3 consecutive days, 2) average of 2 consecutive days, or 3) the volume on day of assessment.
  - Severe abdominal pain, ileus, and/or grossly bloody stool should be documented when present, because Stage 4 lower GI GVHD is staged based on the presence of these symptoms and is independent of volume of diarrhea.

[redacted]

7.6.3. Donor Chimerism

Donor chimerism after a hematopoietic stem cell transplant involves identifying the genetic profiles of the recipient and of the donor and then evaluating the ratio of donor to recipient cells in the recipient's blood, bone marrow, or other tissue. Chimerism testing using peripheral blood or bone marrow will be performed at the treating investigator's discretion according to local institutional practice as indicated in Table 5. In general, genomic polymorphisms should be assessed via polymerase chain reaction analysis of short tandem repeat loci from isolated lymphocytes or myeloid cells. Fluorescence *in situ* hybridization analysis may also be used in cases with sex-mismatched transplants (Matsuda et al 2004).

7.6.4. Post-Transplant Lymphoproliferative Disorder Assessment

Staining for Epstein-Barr virus for PTLD testing will be performed according to local institutional practice at the treating investigator's discretion as indicated in Table 5.

7.7. Pharmacokinetic Assessments

7.7.1. Blood Sample Collection

Pharmacokinetic samples will be obtained on Days 1, 7, and 14. On each of these days, a predose blood sample will be drawn, study treatment will be administered, and serial blood samples will be taken at the intervals shown in Table 9.

The exact date and time of the PK blood draws will be recorded in the eCRF along with the date and time of the last dose of study drug preceding the blood draw (if applicable) and the time of the most recent meal. Instructions for sample preparation and shipping will be provided in the Laboratory Manual. Subjects will receive reminder cards in advance of the study visit providing instruction to hold the dose of study drug on the day of the visit, as well as a place to record the time of the previous dose of study drug and time of the most recent meal or snack consumed.

If PK samples are missing for a subject, PK sample collection should be performed at the next visit. On Days 1, 7, and 14, subjects must refrain from taking study medication before arriving for the visit. Subjects should not have consumed any food within 8 hours before arriving at the clinic. A trough (predose) PK sample (30-minute window) should be drawn at each of the PK visits. Following the trough PK sample, the subject should take the assigned dose of study treatment, and subsequent timed samples will be taken. Food should be withheld until 1 hour after study drug administration.

Table 9: Pharmacokinetic Sample Collection Time and Windows

Study Day	Timing of Sample Relative to INCB018424 Administration			
Day 1	Predose	1 h ± 15 min	2 h ± 30 min	4-8 h
Day 7	Predose	1 h ± 15 min	2 h ± 30 min	4-8 h
Day 14	Predose	1 h ± 15 min	2 h ± 30 min	4-8 h

7.7.2. Bioanalytical Methodology and Analysis

Plasma samples will be analyzed for ruxolitinib by a validated liquid chromatography–tandem mass spectrometry assay. These samples will be analyzed by Incyte Corporation (Wilmington, DE) or its designee.

Pharmacokinetic parameters will be calculated from the plasma concentrations of ruxolitinib according to a model-independent approach or population PK approach. Instructions regarding sample collection, handling, and shipping will be provided in the Laboratory Manual.

[redacted]

7.9. Other Study Procedures

7.9.1. Distribution of Subject Reminder Cards

Subjects will be provided with a reminder card at each visit. The subject reminder card will indicate the date/time of the next visit and will also remind the subject to not take the study drug on Days 1, 7, and 14 until after blood samples for PK and safety have been drawn in the clinic. The reminder cards for the Day 1, 7, and 14 visits will have an area for the subject to record the date and time of the last dose taken (from the previous day) and the time of their last meal before the visit.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related that occurs after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in the study drug(s).

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events form of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF. Monitoring for the occurrence of new AEs should be continued for at least 30 days after the last dose of study drug. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

The term "disease progression" should be recorded as an AE/SAE itself only if there are no other identifiable AEs/SAEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (eg, resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s) as described in Section 8.3.2. In both cases (ie, AEs or SAEs related to disease progression), for each event it should be indicated whether the event (diagnosis or signs and symptoms) is related to disease progression.

The severity of AEs will be assessed using CTCAE v4.03 Grades 1 through 4. The CTCAE v4.03 severity of Grade 5 will not be used; AEs resulting in death will be graded accordingly using Grades 1 through 4 and have the outcome noted as fatal. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimally, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.

The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. To the extent possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 4).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious adverse event (SAE) definition provided in Section 8.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see Section 8.3.2).

All AEs should be treated appropriately. If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on Adverse Event form and the treatment should

be specified on the Prior/Concomitant Medications or Procedures and Non-Drug Therapy form in the eCRF.

Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.

When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE, which lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved. For analysis purposes, this will be considered 1 AE for this subject, and the highest reported severity will be used.

8.2. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug) should be recorded on the Adverse Event form in the eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (eg, "anemia" instead of "low hemoglobin"). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 (severe) AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1, and/or per the investigator's discretion. A dose modification for the laboratory abnormality may be required (see Section 5.4.2) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

An SAE is defined as an event that meets at least 1 of the following criteria:

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.

  - An elective surgery or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.
  - Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.
- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions.
- Constitutes a congenital anomaly or birth defect.
- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

8.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 30 days) after the last dose of study drug, whichever is later) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Any SAEs occurring more than 30 days after the last dose of study drug should be reported to the sponsor or its designee only if the investigator suspects a causal relationship to the study drug.

Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to each specific study drug (ruxolitinib and corticosteroids) during the time it is given.

The investigator must also complete the Incyte Serious Adverse Event Report Form, in English, and send the completed and signed form to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the study treatment: suspected (yes) or not suspected (no). Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.

The contact information of the sponsor's study-specific representatives is listed in the investigator manual provided to each site. The original copy of the SAE Report Form and the confirmation sheet must be kept at the study site.

Investigational site personnel must report any new information regarding the SAE within 24 hours of becoming aware of the information in the same manner that the initial SAE Report Form was sent. Follow-up information is recorded on an amended or new SAE Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous

SAE Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or subject disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a subject during maternal or paternal exposure to study drug, the following procedures should be following in order to ensure subject safety:

- The study drug must be discontinued immediately (female subjects only; see Section 5.4.1 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each 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, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy must be recorded on the SAE report form and submitted to the sponsor or designee.

8.6. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the Investigator's Brochure (IB). Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications (INs). Any important new safety information should be discussed with the subject during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

8.7. Data Monitoring Committee

There is no formal Data Monitoring Committee review.

The sponsor will continuously monitor safety through frequent contact with the treating investigators, review of the clinical data, and formal study meetings. Routine teleconferences will be held among participating study sites to provide subject-by-subject updates on current study status, interim toxicities reported, and any other pertinent information. Adverse event and laboratory data entered into the clinical database will be reviewed periodically for trends and evolving safety signals.

8.8. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be reported as described in Section 8.1.2 of this Protocol.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

9. STATISTICS

9.1. Study Populations

Subject enrollment, disposition, demographics, and medical history will be summarized at baseline. Dose exposure will be calculated for each subject. Safety and disease response data will be compared over time to assess change from baseline, during treatment, and follow-up.

The populations to be analyzed include the following:

- Efficacy Evaluable Population: Subjects enrolled into the study.
- Safety Evaluable Population: Subjects enrolled into the study who received at least 1 dose of study drug.
- Pharmacokinetic Evaluable Population: Subjects who receive at least 1 dose of study drug and provide at least 1 plasma sample (1 PK measurement) after study drug administration will be considered as potential PK evaluable subjects. The study pharmacokineticist will review data listings of study drug administration and sample records to identify subjects to be excluded from analyses of PK data.

9.2. Selection of Sample Size

Approximately 70 subjects are planned for the final analysis of the primary endpoint of ORR. A treatment regimen for steroid-refractory GVHD demonstrating an absolute improvement of 20% versus historic data would be considered clinically meaningful. With the assumed true rate of 60%, a sample size of 70 subjects would provide > 90% probability to have a 95% CI with lower limit of ≥ 40%.

An interim analysis will be conducted when 35 subjects complete the Day 28 visit in order to assess for futility; if the lower boundary is crossed, the study will be terminated.

A group sequential design method for 1 sample binary outcome data will be used to calculate the lower boundary of futility. The spending function of HSD(-4) will be used. For H0: $p = 0.4$, Ha: $p = 0.6$, and a 1-sided binomial test with alpha of 0.025, if ≤ 15 subjects respond at the time of the interim analysis, the study will be terminated. This will provide 70.03% probability for the response rate of 40% at the interim analysis.

If ≥ 37 subjects respond at the time of final analysis, the study outcome will be considered positive. These assumptions will provide 89.88% power for the response rate of 60% in the final analysis with Type I error of 0.0189.

9.3. Level of Significance

No formal statistical tests will be performed. All CIs will be 95%.

9.4. Statistical Analyses

9.4.1. Primary Analyses

The primary endpoint is ORR at Day 28, defined as the proportion of subjects demonstrating a CR, VGPR, or PR, as per standard criteria (Appendix B). The primary analysis will be conducted once the last subject completes the Day 28 visit or withdraws from the study.

Summary statistics and 95% CI will be provided.

9.4.2. Secondary Analyses

The key secondary endpoint is 6-month DOR, defined as the time from first response until GVHD progression or death. Six-month DOR will be assessed when all subjects complete the the Day 180 visit. The duration of disease control will be estimated by the Kaplan-Meier method.

Additional secondary endpoints will be analyzed as follows:

- ORR, defined as the proportion of subjects demonstrating a CR, VGPR, or PR at Days 14, 56, and 100. Summary statistics and applicable 95% CI will be provided.
- Three-month DOR, defined as the time from first response until GVHD progression or death, when all subjects complete the Day 84 visit.
- NRM, defined as the proportion of subjects who died due to causes other than malignancy relapse at Months 6, 9, 12, and 24. Cumulative incidence rates will be provided. Summary statistics and applicable 95% CI will be provided.
- Relapse rate, defined as the proportion of subjects whose underlying malignancy relapses. The cumulative incidence rate and summary statistics will be provided.
- Relapse-related mortality rate, defined as the proportion of subjects whose malignancy relapses and has a fatal outcome. The cumulative incidence rate and summary statistics will be provided.
- FFS, defined as the proportion of subjects who are still alive, have not relapsed, have not required additional therapy for acute GVHD, and have not demonstrated signs or symptoms of chronic GVHD, at Month 6. The Kaplan-Meier method will be used. Summary statistics will be provided.
- Overall survival, defined as the time from study enrollment to death due to any cause. The Kaplan-Meier method will be used. Summary statistics will be provided.
- Clinical safety data (eg, AEs, infections) will be tabulated and listed.
- The plasma PK of ruxolitinib will be analyzed using a model-independent approach.

9.4.4. Safety Analyses

9.4.4.1. Adverse Events

A TEAE is either any AE reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs, regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the NCI CTCAE v4.03.

The subset of AEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, then the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

9.4.4.2. Clinical Laboratory Tests

Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

Laboratory data will be classified into CTC grades for AEs (CTCAE v4.03). The following summaries will be produced for the laboratory data:

- Number and percentage of subjects with worst postbaseline CTC grade (regardless of baseline value) will be summarized. Each subject will be counted only for the worst grade observed postbaseline.

- Shift tables using CTC grades to compare baseline with the worst postbaseline value will be produced with CTC grade.
- For laboratory parameters where CTC grades are not defined, shift tables to the worst postbaseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

9.4.4.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 10), and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

Table 10: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38°C	< 35.5°C
Respiratory rate	> 24/min	< 8/min

9.4.4.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (Table 11). Subjects exhibiting clinically notable ECG abnormalities will be listed. Adverse events will be reported for clinically notable abnormalities that are considered clinically significant in the judgment of the investigator.

Table 11: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 460 msec	< 295 msec
PR	> 220 msec	< 75 msec
QRS	> 120 msec	< 50 msec
QT	> 500 msec	< 300 msec
RR	> 1330 msec	< 600 msec

QTcF = Fridericia correction.

9.4.5. Pharmacokinetic Analysis

The PK parameters of C_{max}, T_{max}, C_{min}, $AUC_{0\text{-}t}$, and CL/F will be calculated from the blood plasma concentrations of ruxolitinib using standard noncompartmental (model-independent) PK methods. Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as WinNonlin® (Pharsight Corporation, Mountain View, CA). Nominal times will be used in all cases, except when the difference between the actual time and nominal time is greater than 15 minutes for samples collected up to 4 hours after administration and greater than

30 minutes for samples collected more than 4 hours after administration; in these cases, actual time will be used for PK analysis.

If there is a sufficient amount of plasma concentration data from this study, then the data will be analyzed by standard population PK methods using appropriate software (eg, NONMEM).

9.5. Analyses for the Data Monitoring Committee

Not applicable.

9.6. Interim Analysis

An interim analysis will be conducted when 35 subjects complete Day 28 visit. In this interim analysis, only futility will be assessed, and the study will be terminated if the lower boundary is crossed.

A group sequential design method for 1 sample binary outcome data will be used to calculate the lower boundary of futility. The spending function of HSD(-4) will be used. For H0: $p = 0.4$, Ha: $p = 0.6$, and a 1-sided binomial test with alpha of 0.025, if ≤ 15 subjects respond at the time of the interim analysis, the study will be terminated. This will provide 70.03% probability for the response rate of 40% at the interim analysis.

If ≥ 37 subjects respond at the time of final analysis, the study outcome will be considered positive. These assumptions will provide 89.88% power for the response rate of 60% in the final analysis with Type I error of 0.0189.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

This study will be performed in accordance with ethical principles that originate in the Declaration of Helsinki and conducted in adherence to the study Protocol; GCPs as defined in Title 21 of the US CFR Parts 11, 50, 54, 56, and 312; ICH E6 GCP consolidated guidelines; and local regulatory requirements as applicable to the study locations.

The investigator will be responsible for:

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and subject records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all subjects.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.
- Obtaining informed consent and ensuring that the study subjects' questions have been answered and the subjects fully understand study procedures:
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the subject. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records.

- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, important protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.
  - The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by the IRB/IEC.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling subjects who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

10.2. Accountability, Handling, and Disposal of Study Drug

The investigator is responsible for drug accountability at the study site; however, some of the drug accountability duties may be assigned to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Subject use of the study drug including pill or unit counts from each supply dispensed.
- Return of study drug to the investigator or designee by subjects.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the specified

study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study subjects.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

10.3. Data Management

Data management will be performed in a validated database via an Electronic Data Capture (EDC) system. All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of the Data Management Department at the sponsor or its designee. The database will be authorized for lock once all defined procedures are completed.

The investigator will be provided with access to an EDC system so that an eCRF can be completed for each subject. Entries made in the eCRF must be verifiable against source documents; if updates to the database are not possible, any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and eCRF entries and will sign and date the designated forms in each subject's eCRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all query responses.

Protocol deviations will be identified and recorded in the Protocol Deviation form of the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

10.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor, or its designee, must adhere to data privacy laws and regulations. The investigator and the sponsor, or its designee, are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Subject names will not be supplied to the sponsor or its designee, if applicable. Only the subject number and subject's initials (subject's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where permitted; if the subject's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor or its designee, IRB or IEC, or regulatory authorities may inspect their medical

records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

10.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 Code of Federal Regulations (CFR) Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

10.6. Publication Policy

By signing the study Protocol, the investigator and his or her institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - injectable
  - implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Source: CTFG 2014.

Appendix B. MAGIC GUIDELINES FOR STAGING AND GRADING ACUTE GVHD

Acute GVHD Staging and Grading, MAGIC Guidelines

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper GI	Lower GI (Stool Output/Day)
0	No active (erythematous) GVHD rash	< 2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: < 500 mL/day or < 3 episodes/day. Child: < 10 mL/kg per day or < 4 episodes/day.
1	Maculopapular rash < 25% BSA	2-3 mg/dL	Persistent nausea, vomiting, or anorexia	Adult: 500-999 mL/day or 3-4 episodes/day. Child: 10-19.9 mL/kg per day or 4-6 episodes/day.
2	Maculopapular rash 25%-50% BSA	3.1-6 mg/dL	–	Adult: 1000-1500mL/day or 5-7 episodes/day. Child: 20-30 mL/kg per day or 7-10 episodes/day.
3	Maculopapular rash > 50% BSA	6.1-15 mg/dL	–	Adult: > 1500 mL/day or > 7 episodes/day. Child: > 30 mL/kg per day or > 10 episodes/day.
4	Generalized erythroderma (>50%) with bullae	> 15 mg/dL	–	Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume).

Overall clinical grade (based on most severe target organ involvement):
Grade 0: No stage 1-4 of any organ.
Grade I: Stage 1-2 skin without liver, upper GI, or lower GI involvement.
Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
Grade III: Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI.
Grade IV: Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI.

Response Definitions:

GVHD response assessments will be made with respect to changes in the organ stage relative to Study Day 1.

- Complete response (CR) is defined as a score of 0 for the GVHD grading in all evaluable organs. For a response to be scored as CR at Day 28 or later, the participant must still be in CR on that day and have had no intervening additional therapy for an earlier progression, mixed response (MR), or no response (NR).
- Very good partial response (VGPR) is defined as follows:
  - Skin: No rash, or residual erythematous rash involving < 25% of the body surface, without bullae (residual faint erythema and hyperpigmentation do not count).
  - Liver: Total serum bilirubin concentration < 2 mg/dL or < 25% of baseline at enrollment.
  - Gut:
    - Tolerating food or enteral feeding.
    - Predominantly formed stools.
    - No overt gastrointestinal bleeding or abdominal cramping.
    - No more than occasional nausea or vomiting.
- Partial response (PR) is defined as improvement in 1 stage in 1 or more organs involved with GVHD symptoms without progression in others. For a response to be scored as PR at Day 28 or later, the participant must still be in PR on that day and have had no intervening additional therapy for an earlier progression, MR, or NR.
- Mixed response is defined as improvement in 1 or more organs with deterioration in another organ manifesting symptoms of GVHD or development of symptoms of GVHD in a new organ.
- Progression of disease is defined as deterioration in at least 1 organ without any improvement in others.
- No response is defined as absence of any improvement or progression as defined. Subjects receiving secondary therapy (including need to re-escalate steroid dose to greater than the Day 1 dose) will be classified as nonresponders.

Source: CIBMTR 2009, Martin et al 2009, Harris et al 2016.

APPENDIX C. CYTOCHROME P450 AND P-GLYCOPROTEIN INHIBITORS AND CYTOCHROME P450 INDUCERS

University of Washington School of Pharmaceutics: Drug Interaction Database Program. 2002. http://www.druginteractioninfo.org. Accessed May 2015. Highlighted rows indicate recent additions to the lists at the time the database search was performed.

In Vivo CYP3A Inhibitors

Inhibitor	Therapeutic Class	Inhibitor dosing (oral)	Object[1] (oral, unless otherwise specified)	AUC_{ratio}	PMID or NDA #	Published
Potent CYP3A Inhibitors (yielding substrate AUCr > 5)						
indinavir /RIT	Protease Inhibitors	800/100 mg BID (1 day)	alfentanil	36.5	19225389	2009 Mar
tipranavir/RIT	Protease Inhibitors	500/200 mg BID (2 days)	midazolam	26.91	20147896	2010 Jun
ritonavir	Protease Inhibitors	3 doses of 100 mg over 24 h	midazolam	26.41	20002087	2009 Dec
cobicistat (GS-9350)	None	200 mg QD (14 days)	midazolam	19.03	20043009	2010 Mar
indinavir	Protease Inhibitors	800 mg TID (7 days)	vardenafil	16.25	NDA # 021400	2003 Aug
ketoconazole	Antifungals	400 mg QD (4 days)	midazolam	15.9	8181191	1994 May
troleandomycin	Antibiotics	500 mg single dose	midazolam	14.8	15536460	2004 Dec
telaprevir	Antivirals	750 mg TID (16 days)	midazolam	13.5	22162542	2012 Oct
danoprevir / RIT	Antivirals	200/100 mg QD (14 days)	midazolam	13.42	23872824	2013 Nov
elvitegravir / RIT	Treatments of AIDS	150/100 mg QD (10 days)	midazolam	12.8	NDA # 203100	2012
saquinavir / RIT	Protease Inhibitors	1000/100 mg BID (14 days)	midazolam	12.48	19792991	2009 Oct
lopinavir / RIT	Protease Inhibitors	400/100 mg BID (2 days)	alfentanil	11.47	24067429	2013 Dec
itraconazole	Antifungals	200 mg QD (4 days)	midazolam	10.8	8181191	1994 May
voriconazole	Antifungals	200 mg BID (9 days)	midazolam	9.63	21937987	2011 Nov
mibefradil	Calcium Channel Blockers	100 mg single dose	midazolam	8.86	14517191	2003 Oct
LCL161	Cancer Treatments	600 mg single dose	midazolam	8.8	23585187	2013 Jun
clarithromycin	Antibiotics	500 mg BID (7 days)	midazolam	8.39	16432272	2006 Feb
posaconazole	Antifungals	400 mg BID (7 days)	midazolam	6.23	19302901	2009 Feb
telithromycin	Antibiotics	800 mg QD (6 days)	midazolam	6.2	NDA# 021144	2004
grapefruit juice DS[2]	Food Products	240 mL TID (2 days) and 90 min, 60 min, 30 min prior to midazolam	midazolam	5.95	12953340	2003 Aug
conivaptan	Diuretics	40 mg BID (5 days)	midazolam	5.76	NDA # 021697	2005
nefazodone	Antidepressants	100-200 mg BID (12 days)	midazolam	5.44	14551182	2003 Nov
nelfinavir	Protease Inhibitors	1250 mg BID (14 days)	midazolam	5.29	21406602	2011 Jun
saquinavir	Protease Inhibitors	1200 mg TID (5 days)	midazolam	5.18	10430107	1999 Jul
idelalisib	Kinase Inhibitors	150 mg BID (8 days)	midazolam	5.15	NDA # 206545	2014
boceprevir	Antivirals	800 mg TID (6 days)	midazolam	5.05	NDA # 202258	2011
Moderate CYP3A Inhibitors (AUCr ≥ 2 and < 5)						
erythromycin	Antibiotics	1000 mg single dose	midazolam	4.99	25139487	2014 Dec
fluconazole	Antifungals	400 mg single dose	midazolam	4.93	16172184	2005 Oct
atazanavir / RIT	Protease Inhibitors	300/100 mg BID	maraviroc	4.9	18333863	2008 Apr
darunavir	Protease Inhibitors	1200 mg BID (14 days)	saquinavir	4.9	NDA # 021976	2006
diltiazem	Calcium Channel Blockers	60 mg TID (2 days)	midazolam	4.06	21209240	2011 Nov
darunavir / RIT	Protease Inhibitors	400/100 mg BID (8 days)	sildenafil	4.0	NDA # 021976	2006
dronedarone	Antiarrhythmics	400 mg BID (14 days)	simvastatin	3.66	NDA # 022425	2009
crizotinib	Kinase Inhibitors	250 mg BID (28 days)	midazolam	3.65	NDA # 202570	2011
atazanavir	Protease Inhibitors	400 mg QD (7 days)	maraviroc	3.57	18333863	2008 Apr
aprepitant	Antiemetics	80-125 mg QD (5 days)	midazolam	3.29	12891225	2003 Aug
casopitant	Antiemetics	120 mg QD (14 days)	midazolam	3.13	20840445	2010 Oct
amprenavir	Protease Inhibitors	1200 mg BID (10 days)	rifabutin	2.93	11158747	2001 Feb
imatinib	Antineoplastic Agents	400 mg QD (7 days)	simvastatin	2.92	14612892	2003 Nov
verapamil	Calcium Channel Blockers	80 mg TID (2 days)	midazolam	2.92	8198928	1994 Mar
ledipasvir	Antivirals	30 mg QD (10 days)	simeprevir	2.69	NDA # 205123	2013
netupitant	Antiemetics	300 mg single dose	midazolam	2.44	23729226	2013 Oct
grapefruit juice	Food Products	240 mL QD (4 days)	midazolam	2.39	10546919	1999 Oct
tofisopam	Benzodiazepines	100 mg TID (9 days)	midazolam	2.36	17989974	2008 Jan
cyclosporine	Immunosuppressants	Not provided (1-5 years)	midazolam	2.21	21753749	2011 Sep
ACT-178882	Renin Inhibitors	300 mg QD (14 days)	midazolam	2.19	22849770	2013 Dec
ciprofloxacin	Antibiotics	500 mg single dose	sildenafil	2.12	16372380	2005 Dec
schisandra sphenanthera	Herbal Medications	3 capsules (= 11.25 mg deoxyschizandrin) BID (7 days)	midazolam	2.05	19552749	2009 May

cimetidine	H-2 Receptor Antagonists	200-400 mg QID (1.5 days)	midazolam	2.02	6152615	1984 Sep
FK1706	Central Nervous System Agents	60 mg QD (14 days)	midazolam	2.01	19889885	2010 Feb
lomitapide	Other Antilipemics	60 mg QD (7 days)	simvastatin	2.0	NDA # 203858	2012
		Weak CYP3A Inhibitors (AUCr ≥ 1.25 and < 2)				
tabimorelin	Hormone Replacement	2.86-3.21 mg QD (7 days)	midazolam	1.93	12610745	2003 Feb
ranolazine	Cardiovascular Drugs	1000 mg BID (7 days)	simvastatin	1.89	NDA # 021526	2006
amlodipine	Calcium Channel Blockers	10 mg QD (9 days)	simvastatin	1.8	23965645	2014 Apr
lomitapide	Other Antilipemics	60 mg QD (7 days)	simvastatin	1.77	24734312	2014 Mar
fosaprepitant (IV)	Antiemetics	150 mg single 30-min infusion	midazolam	1.76	21209230	2011 Dec
Seville orange juice	Food Products	240 mL single dose	felodipine	1.76	11180034	2001 Jan
amiodarone	Antiarrhythmics	400 mg QD (4 days)	simvastatin acid	1.76	17301736	2007 May
chlorzoxazone	Muscle Relaxants	250 mg single dose (part of a 6-drug cocktail)	midazolam	1.68	11736864	2001 Nov
M100240	Antihypertensive Agents	50 mg single dose	midazolam	1.66	15051745	2004 Apr
fluvoxamine	Antidepressants	50-00 mg BID (12 days)	midazolam	1.66	14551182	2003 Nov
ranitidine	H-2 Receptor Antagonists	150 mg BID (1.5 days)	midazolam	1.66	6135440	1983 Jun
goldenseal	Herbal Medications	1,323 mg (= 24.1 mg isoquinoline alkaloids) TID (14 days)	midazolam	1.63	17495878	2008 Jan
clotrimazole	Antifungals	10 mg TID (5 days)	midazolam	1.61	20233179	2010 Feb
tacrolimus	Immunosuppressants	Not provided (1-5 years)	midazolam	1.61	21753749	2011 Sep
cilostazol	Antiplatelets	100 mg BID (7 days)	lovastatin	1.56	10702889	1999
ticagrelor	Antiplatelets	180 mg bid (7 days)	simvastatin	1.56	NDA # 022433	2011
peppermint oil	Food Products	600 mg (= 300 uL peppermint oil) single dose	felodipine	1.55	12235445	2002 Sep
ivacaftor	Cystic fibrosis treatments	150 mg BID (6 days)	midazolam	1.54	NDA # 203188	2012
GSK2248761	Transcriptase Inhibitors	100 mg QD (12 days)	midazolam	1.54	22288567	2012 Aug
roxithromycin	Antibiotics	300 mg QD (6 days)	midazolam	1.47	7995324	1994
suvorexant	Hypnotics - Sedatives	80 mg QD (14 days)	midazolam	1.47	NDA # 204569	2014
propiverine	Anticholinergics	15 mg BID (7 days)	midazolam	1.46	16183781	2005 Dec
isoniazid	Antibiotics	90 mg BID (4 days)	triazolam	1.46	6140941	1983 Dec
berberine	Herbal Medications	300 mg TID (14 days)	midazolam	1.45	21870106	2012 Feb
oral contraceptives	Oral contraceptives	OC with low doses of estrogen (< 35 ug ethinylestradiol) (> 3 months)	triazolam	1.44	6149030	1984 Nov
delavirdine	NNRTIs	400 mg TID (9 days)	indinavir	1.44	9665503	1998 Jul
daclatasvir	Antivirals	60 mg QD (7 days)	simeprevir	1.44	NDA # 205123	2013
faldaprevir	Antivirals	240 mg BID (8 days)	ethinyl estradiol	1.44	25385099	2015 Jan
simeprevir	Protease Inhibitors	150 mg QD (11 days)	midazolam	1.43	NDA # 205123	2013
atorvastatin	HMG CoA Reductase Inhibitors (Statins)	10-40 mg/day (chronic treatment)	midazolam IV	1.41	12911366	2003 Sep
tolvaptan	Vasopressin Antagonists	60 mg single dose	lovastatin	1.41	NDA # 022275	2009
almorexant	Hypnotics - Sedatives	200 mg QD (9 days)	midazolam	1.37	22990330	2013 Mar
GSK1292263	Other Antilipemics	300 mg BID (9 days)	simvastatin	1.36	23256625	2013 Jun
linagliptin	Dipeptidyl Peptidase 4 Inhibitors	10 mg QD (6 days)	simvastatin	1.34	20497745	2010 Jun
resveratrol	Food Products	1 g QD (4 weeks)	buspirone	1.33	20716633	2010 Sep
lacidipine	Calcium Channel Blockers	4 mg QD (8 days)	simvastatin	1.33	11259986	2001 Feb
cranberry juice	Food Products	240 mL double strength juice, 1 glass q 15 min x 3	midazolam	1.33	19114462	2009 Mar
pazopanib	Kinase Inhibitors	800 mg QD (17 days)	midazolam	1.32	20881954	2010 Nov
everolimus	Immunosuppressants	10 mg QD (5 days)	midazolam	1.31	23426978	2013 Apr
blueberry juice	Food Products	two doses of 300 mL, separated by 16 hours	buspirone	1.31	22943633	2013 Apr
nilotinib	Kinase Inhibitors	600 mg single dose	midazolam	1.3	NDA # 022068	2007
AMD070	Fusion Inhibitors	200 mg BID (8 days)	midazolam	1.29	18362694	2008 Apr
alprazolam	Benzodiazepines	1 mg TID (7 days)	buspirone	1.29	8300893	1993 Nov
bicalutamide	Antiandrogens	150 mg QD (>3 months)	midazolam	1.27	15509184	2004
sitaxentan	Endothelin Receptor Antagonists	100 mg QD (7 days)	sildenafil	1.27	20078609	2010 Jan
azithromycin	Antibiotics	500 mg QD (3 days)	midazolam	1.27	8720318	1996 Feb
ginkgo	Herbal Medications	120 mg TID (28 days)	midazolam	1.25	17050793	2006 Nov
teriflunomide	Other Immunomodulators	14-70 mg QD (14 days)	midazolam	1.25	NDA # 202992	2012

[1] To allow better comparability, DDI studies with the probe substrate midazolam were selected first.
When no study with midazolam was available, the AUCratio of another probe or sensitive substrate is presented.
[2] 240 mL GFJ double-strength administered TID for 3 days

In Vivo CYP3A Inducers

Inducers	Therapeutic class	Object (oral, unless otherwise specified)	% ↓ AUC	% ↑ oral CL	Precipitant Dose (oral)	PMID or NDA #	Published
Potent Inducers (AUC decreased by ≥ 80% or CL increased by more than 5 fold (400%))							
rifampin	Antibiotics	budesonide	99.7	36904.5	600 mg QD (7 days)	15726657	2005 Mar
mitotane	Other Antineoplastics	midazolam	94.5	Not Provided	maximum of 3.5 g TID (chronic therapy)	21220434	2011 Apr
avasimibe	Other Antilipemics	midazolam	93.5	Not Provided	750 mg/day (7 days)	12766253	2003 Sep
phenytoin	Anticonvulsants	nisoldipine	89.5	Not Provided	200-450 mg/day (chronic treatment)	8917062	1996 Nov
carbamazepine	Anticonvulsants	quetiapine	86.6	643.1	200 mg TID (26 days)	16390352	2006 Jan
enzalutamide	Antiandrogens	midazolam	85.9	Not Provided	160 mg QD (85±3 days)	NDA # 203415	2012
St John's Wort	Herbal Medications	midazolam	80.0	Not Provided	300 mg TID (14 days)	16341856	2006 Jan
rifabutin	Antibiotics	delavirdine	Not Provided	458.0	300 mg QD (14 days)	9224961	1997 Jun
phenobarbital	Anticonvulsants	verapamil	76.6	400.9	100 mg QD (21 days)	3392664	1988 Jul
Moderate Inducers (AUC decreased by 50-80% or CL increased by 2-5 fold (100-400%))							
ritonavir and St. Johns wort	None	midazolam	77.2	Not Provided	ritonavir: 300 mg BID and SJW: 300 mg TID (14 days)	19924124	2010 Feb
semagacestat	Alzheimer's Treatments	midazolam	76.4	324.6	140 mg QD (10 days)	22789530	2012 Oct
efavirenz	NNRTIs	alfentanil	76	369.4	600 mg QD (20 days)	22398970	2012 Apr
tipranavir and ritonavir	Protease Inhibitors	saquinavir	75.6	Not Provided	tipranavir: 500 mg and ritonavir: 200 mg BID (14 days)	18176328	2008 Apr
bosentan	Endothelin Receptor Antagonists	sildenafil	69.0	239.8	62.5-125 mg BID (8 weeks)	15963102	2005 Jul
genistein	Food Products	midazolam	13.7	136.9	1000 mg QD (14 days)	21943317	2012 Feb
thioridazine	Antipsychotics	quetiapine	68.7	104.5	100-300 mg QD (15 days)	22569350	2012 Jun
nafcillin	Antibiotics	nifedipine	62.6	145.1	500 mg 4 times daily (5 days)	12814453	2003 Jun
talviraline	NNRTIs	indinavir	61.7	181.2	500 mg TID (14 days)	10516944	1999 Oct
lopinavir	Protease Inhibitors	amprenavir	59.7	Not Provided	400 mg BID (4 weeks)	15060509	2004 Apr
modafinil	Psychostimulants	triazolam	57.6	35.7	200-400 mg QD (28 days)	11823757	2002 Jan
etravirine	NNRTIs	sildenafil	56.7	Not Provided	800 mg BID (13.5 days)	NDA# 022187	2008
lersivirine	NNRTIs	midazolam	51.4	105.5	1000 mg BID (14 days)	22527351	2012 Nov
Weak Inducers (AUC decreased by 20-50% or CL increased by less than 2 fold (100%))							
eslicarbazepine	Anticonvulsants	simvastatin	49.4	98.4	800 mg QD (14 days)	23726291	2013 Sep
telaprevir	Antivirals	darunavir	48.4	Not Provided	1125 mg BID (4 days)	NDA# 201917	2011
garlic	Food Products	saquinavir	44.7	Not Provided	caplet of GarliPure BID (20 days)	11740713	2002 Jan
bexarotene	Other Antineoplastics	atorvastatin	45.3	Not Provided	400 mg/m2 QD (at least two 4-week cycles)	22057855	2012 Feb
amprenavir	Protease Inhibitors	lopinavir	43.0	Not Provided	700 mg BID (2-4 weeks)	15668539	2005 Jan
raltegravir	HIV-Integrase Strand Transfer Inhibitors	darunavir	42.0	Not Provided	400 mg BID	21958880	2012 Feb
vemurafenib	Kinase Inhibitors	midazolam	39.4	Not Provided	960 mg BID (15 days)	NDA # 202429	2011
troglitazone	Thiazolidinediones	simvastatin	37.7	Not Provided	400 mg QD (24 days)	11361054	2001 May
sorafenib	Kinase Inhibitors	sirolimus	36.9	Not Provided	200 mg BID (11 days)	21045832	2010 Nov
rufinamide	Anticonvulsants	triazolam	36.7	53.4	400 mg BID (11.5 days)	NDA # 021911	2008
pleconaril	Antivirals	midazolam	34.6	52.8	400 mg TID (6 days)	16467135	2006 May
ginseng	Herbal Medications	midazolam	34.2	50.7	500 mg BID (28 days)	21646440	2012 Jun
boceprevir	Antivirals	darunavir	34.2	41.0	800 mg every 8 hrs (6 days)	23155151	2013 Mar
sulfinpyrazone	Antigout and Uricosuric Agents	cyclosporine	33.9 (change in C_{ave})		200 mg/day	11124491	2000 Dec
gingko	Herbal Medications	midazolam	33.7	52.6	120 mg BID (28 days)	18205997	2008 Feb
vinblastine	Vinca Alkaloids	midazolam IV	33.2	48.8	not provided (4 cycles)	20959500	2010 Nov
nevirapine	NNRTIs	indinavir	32.5	Not Provided	200 mg QD (14 days), then BID (19 days)	10191212	1999 May
armodafinil (R-modafinil)	Psychostimulants	midazolam	32.2	54.7	100-250 mg/day (31 days)	18076219	2008
ticagrelor	Anticoagulants and Antiplatelets	midazolam	31.7	46.5	400 mg QD (6 days)	23870610	2013 Jul
LCL161	Cancer Treatments	midazolam	29.8	34.0	600 mg single dose	23585187	2013 Jun
vicriviroc and ritonavir	Treatments of AIDS	ethinyl estradiol	29.4	Not Provided	30 mg vicriviroc and 100 mg ritonavir QD (10 days)	22015327	2011 Oct

ritonavir	Protease Inhibitors	ethinyl estradiol	**29.2**	Not Provided	100 mg QD (10 days)	22015327	2011 Oct
prednisone	Corticosteroids	tacrolimus	**29.0**	Not Provided	1.5 mg/kg/day	15787787	2005 Apr
oxcarbazepine	Anticonvulsants	felodipine	**28.1**	Not Provided	450 mg BID (7 days)	8451779	1993 Feb
danshen	Herbal Medications	midazolam	**27.9**	**32.8**	4 g TID (14 days)	20565457	2010 Jun
clobazam	Benzodiazepines	midazolam	**27.7**	Not Provided	40 mg QD (15 days)	22422635	2012 Apr
echinacea	Herbal Medications	midazolam	**27.3**	**37.5**	500 mg TID (28 days)	20393696	2010 Aug
ticlopidine	Anticoagulants and Antiplatelets	alfentanil	**27.0**	**50.0**	250 mg BID (4 days)	23361846	2013 Mar
brivaracetam	Anticonvulsants	ethinyl estradiol	**26.8**	**37.3**	200 mg BID (21 days)	24386664	2013 Dec
Stribild*	Treatments of AIDS	ethinyl estradiol	**26.2**	**31.3**	150 mg ELV + 150 mg COB + 200 mg EMT+ 300 mg TEN	NDA # 203100	2012
pioglitazone	Thiazolidinediones	midazolam	**26.0**	Not Provided	45 mg QD 7 days	Actos® Product Label	
dexamethasone	Corticosteroids	aprepitant	**25.0**	Not Provided	8 mg/day (5 days)	NDA # 021549	2003
terbinafine	Antifungals	midazolam	**24.5**	Not Provided	250 mg QD (4 days)	8527290	1995 Sep
quercetin	Food Products	midazolam	**23.6**	Not Provided	500 mg QD (13 days)	21680781	2012 Jun
glycyrrhizin	Herbal Medications	midazolam	**23.0**	Not Provided	150 mg BID (15 days)	20393696	2010 Aug
aprepitant	Neurokinin-1 Receptor Antagonists	midazolam IV	**22.1**	**28.5**	125/80 mg QD (3 days)	14973304	2004 Mar
PA-824	Antibiotics	midazolam	**22.1**	**20.7**	400 mg QD (14 days)	23689718	2013 Aug
oritavancin	Antibiotics	midazolam	**18.7**	**23.9**	1200 mg IV single infusion	NDA # 206334	2014
AZD 7325	Anxiolytics	midazolam	**18.7**	**22.6**	10 mg QD (12 days)	22122233	2012 Jul
methylprednisolone	Corticosteroids	cyclosporine	**15.8**	**35.0**	16 mg/day (12 days) then 8 mg/day (6 months)	12164891	2002 Sep
topiramate	Anticonvulsants	ethinyl estradiol	**12.0**	**20.2**	50 mg/day (21 days)	12681003	2003 Apr

1- Ritonavir has dual effects of simultaneous CYP3A inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity.

2- All the substrates presented in the table are sensitive CYP3A substrates (see definition in FDA guidance) except verapamil, cyclosporine, ethinyl estradiol, and delavirdine.

* **Stribild** is a combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF

Signature Manifest

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Rejection Collaboration

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