Official Title: A Phase 2, Open-Label, Monotherapy, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects With Myeloid/Lymphoid Neoplasms With FGFR1 Rearrangement

NCT Number: NCT03011372

Document Date: Protocol INCB 54828-203 Am 6 Version 6 13 JUL 2023

Clinical Study Protocol

INCB 54828-203

A Phase 2, Open-Label, Monotherapy, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects With Myeloid/Lymphoid Neoplasms With FGFR1 Rearrangement

Product:	**INCB054828 (pemigatinib)**
IND Number:	**131,608**
EudraCT Number:	**2016-002596-10**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803 USA**
Original Protocol (Version 0):	**28 JUN 2016**
Amendment (Version) 1:	**09 AUG 2016**
Amendment (Version) 2:	**12 DEC 2016**
Amendment (Version) 3:	**17 MAY 2018**
Amendment (Version) 4:	**22 MAY 2019**
Amendment (Version) 5:	**02 JUL 2020**
Amendment (Version) 6:	**13 JUL 2023**

INVESTIGATOR'S AGREEMENT

I have read the INCB 54828-203 Protocol (Amendment 6 dated 13 JUL 2023) 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.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

SYNOPSIS

Name of Investigational Product: INCB054828 (pemigatinib)

Title of Study: A Phase 2, Open-Label, Monotherapy, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects With Myeloid/Lymphoid Neoplasms With FGFR1 Rearrangement

Protocol Number: INCB 54828-203	**Study Phase:** 2

Indication: Myeloid/lymphoid neoplasms with FGFR1 rearrangement

Primary Objective:

The primary objective of this study is to evaluate the efficacy of pemigatinib in subjects with myeloid/lymphoid neoplasms with fibroblast growth factor receptor (FGFR) 1 rearrangement.

Secondary Objective:

The secondary objective is to evaluate the safety of pemigatinib in subjects with myeloid/lymphoid neoplasms with FGFR1 rearrangement.

Exploratory Objective:

[redacted]

Primary Endpoint:

The primary endpoint of this study is the proportion of subjects who achieve complete response (CR) as determined by investigator assessment according to the response criteria listed in Appendix E.

Secondary Endpoints:

The secondary endpoints for this study are as follows:

- The proportion of subjects who achieve response, defined as a best response of CR or partial response (PR), as determined by investigator assessment according to the response criteria in Appendix E.
- The proportion of subjects who achieve a complete cytogenetic response (CCyR) as assessed by local analysis and investigator evaluation.
- The proportion of subjects who achieve a partial cytogenetic response (PCyR) as assessed by local analysis and investigator evaluation.
- Duration of CR.
- Duration of response.
- Progression-free survival.
- Overall survival.
- Safety and tolerability, as assessed by evaluating the frequency, duration, and severity of adverse events; through review of findings of physical examinations, changes in vital signs, and electrocardiograms (ECGs); and through clinical laboratory blood and urine sample evaluations.

Exploratory Endpoints:

[redacted]

[redacted]

Overall Study Design:

This is an open-label, monotherapy study of pemigatinib in subjects with myeloid/lymphoid neoplasms with FGFR1 rearrangement. Subjects will receive a once daily (QD) dose of pemigatinib at 13.5 mg on a 2-week-on–therapy and 1-week-off–therapy schedule. With Protocol Amendment 3, the administration schedule was adjusted, and newly enrolled subjects will receive pemigatinib at 13.5 mg continuous administration (no planned dose hold). Subjects receiving treatment under previous versions of the Protocol may be switched to continuous administration after completing at least 3 cycles if there are no ongoing Grade 2 or higher related TEAEs. The written request to switch to continuous administration should be sent to the sponsor's medical monitor.

With Protocol Amendment 4, up-titration of pemigatinib was introduced. In any subject who has not had a serum phosphate level of > 5.5 mg/dL, the investigator will increase the daily dose to 18 mg provided that medical monitor approval is secured and the subject has been on study drug for at least 1 cycle, has been compliant with taking study drug, and has no ongoing Grade 2 or higher treatment-related TEAE.

All potential subjects must have documentation of an 8p11 translocation known to activate FGFR1 through the site's own cytogenetics laboratory. Once documentation has been provided, the subject will then undergo screening to meet the rest of the inclusion/exclusion criteria. Once a subject has completed screening and has enrolled into the study, treatment will start on Cycle 1 Day 1. Subjects will undergo regular safety assessments during treatment as well as regular efficacy assessments.

Subjects will be allowed to continue administration in 21-day cycles until study treatment withdrawal criteria are met.

Study Population:

Subjects with myeloid/lymphoid neoplasms with FGFR1 rearrangement.

Key Inclusion Criteria:

- Men and women, aged 18 or older.
- Documented lymphoid or myeloid neoplasm with 8p11 rearrangement known to lead to FGFR1 activation, based on standard diagnostic cytogenetic evaluation performed locally, before signing informed consent for this study.
- Eligible subjects must:
  - Have relapsed after stem cell transplantation or after other disease modifying therapy, OR
  - Not be current candidates for stem cell transplantation or other disease modifying therapies.

    Note: All relapsed/refractory subjects must have evidence of either cytogenetic or hematological disease and have no evidence of residual toxicity (eg, graft-versus-host disease requiring treatment).
- Life expectancy ≥ 12 weeks.
- ECOG performance status 0 to 2.

Key Exclusion Criteria:

- Prior receipt of a selective FGFR inhibitor.
- History of calcium and phosphate hemostasis disorder or systemic mineral imbalance with ectopic calcification of soft tissues (exception: commonly observed calcifications in soft tissues, such as the skin, kidney, tendons, or vessels due to injury, disease, and aging, in the absence of systemic mineral imbalance).
- Current evidence of clinically significant corneal disorder/keratopathy (including but not limited to bullous/band keratopathy, corneal abrasion, inflammation/ulceration, and keratoconjunctivitis, etc) or retinal disorder (including but not limited to macular/retinal degeneration, diabetic retinopathy, retinal detachment, etc) as confirmed by ophthalmologic examination.
- Use of any potent cytochrome P450 3A4 inhibitors or inducers within 14 days or 5 half-lives (whichever is shorter) before the first dose of study drug.

Pemigatinib, Dosage, and Mode of Administration:

Pemigatinib will be self-administered as a QD oral treatment on a 2-weeks-on–therapy and 1-week-off–therapy schedule or continuous administration (no planned dose hold). Each dose of pemigatinib should be taken as soon as possible after rising with or without food. Tablets will be available in strengths of [redacted] mg and 4.5 mg. The starting dose will be 13.5 mg. One cycle will be defined as 21 days of treatment.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Study Schedule/Procedures:

Subjects will have regularly scheduled study visits at the clinical site as part of a 21-day cycle. Study visits are as follows:

- Screening: Day -28 through Day -1
- Cycle 1: Days 1, 8, and 15 (± 3 days)
- Cycles 2+: Day 1 (± 3 days) of each cycle or Day 1 (± 3 days) of every third cycle (with telemedicine visits conducted in between) when subject has reached the long-term treatment visit schedule (after completing Cycle 18).
- End of treatment (EOT): Upon permanently discontinuing study drug
- Safety follow-up: 30 days (+ 5 days) from date of last dose
- Disease status: Follow subject per standard of care until documented progression
- Survival follow-up: Every 12 (+2) weeks

Laboratory Tests:

Study visits will include sample collection for chemistry, hematology, coagulation, lipid panel, endocrine monitoring, and urinalysis testing. As of Protocol Amendment 6, lipid panel will only be analyzed at Cycle 1 Day 1. Additionally, hepatitis screening (serology) will be done at screening, and pregnancy testing will be done at screening, Day 1 of every cycle before dose administration, and EOT. Subjects who underwent hematopoietic stem cell transplant during the study will continue to have hematology blood tests done concomitantly with the bone marrow assessments.

Central Laboratory:

A sample of bone marrow aspirate or peripheral blood will be sent to the central laboratory for confirmation of FGFR1 rearrangement as well as a central pathology laboratory for analysis. In addition, sites will need to provide peripheral blood and bone marrow slides (core and aspirate whenever possible) at baseline and at the disease assessment timepoints and send them to a central pathology group for review.

Clinical Assessments:

Adverse event assessments, physical examinations, vital signs, ECGs, comprehensive eye examinations, ECOG performance status, and disease response assessments will be performed by the investigative site.

Estimated Duration of Participation:

Once the subject's eligibility has been confirmed through the site's laboratory, screening may begin. Up to 28 days are allowed for screening, followed by continuous treatment in consecutive 21-day cycles as long as the subject is receiving benefit (as judged by treating physician) and has not met any criteria for study withdrawal. Safety follow-up is 30 days (+ 5 days) after the last dose of the study drug. In addition, subjects will be followed for overall survival after stopping treatment with study drug. Study participation is expected to average approximately 6 months per individual subject.

Estimated Number of Subjects:

Approximately 46 subjects will be enrolled.

Principal Coordinating Investigator:

[redacted]

Statistical Methods:

Approximately 46 subjects are planned for the final analysis of the primary endpoint of overall CR rate. With the assumed rates of 35% for the intervention, a sample size of 46 subjects would provide > 80% probability to have a 95% confidence interval with lower limit of > 15% assuming 10% loss to follow-up.

The overall CR rate, defined as the proportion of subjects who achieve a best overall response (BOR) of CR as determined by investigator assessment, will be estimated with 95% CI. Likewise, the proportion of subjects who achieve response, defined as BOR of CR or PR, as determined by investigator assessment, the proportions of subjects who achieve BOR of CCyR and the proportion of subjects who achieve BOR of PCyR, as assessed by local analysis will also be estimated with 95% CI. The progression-free survival, duration of CR, duration of response, and overall survival will be analyzed by the Kaplan-Meier method. Descriptive statistics will be summarized for safety data and for the number of subjects with SD who achieve complete hematological response, marrow response, or clinical benefit, according to investigator assessment.

Data Monitoring Committee:

No independent Data Monitoring Committee is planned for this study. A study committee may be established and include the investigators or designees, the sponsor representatives (eg, medical monitor), and, when appropriate, ad hoc experts.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

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

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BOR	best overall response
CBC	complete blood count
CCyR	complete cytogenetic response
CFR	Code of Federal Regulations
CHR	complete hematologic response
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMD	extramedullary disease
EMS	eosinophilia myeloproliferative syndrome
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	end of treatment
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation	Definition
HDL	high-density lipoprotein
HED	human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act of 1996
HP	hyperphosphatemia
HSCT	hematopoietic stem cell transplant
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
J-GCP	Japan-Good Clinical Practice
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MLN	myeloid/lymphoid neoplasm
MPN	myeloproliferative neoplasm
MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment Form
NOAEL	no-observed-adverse-effect level
OCT	optical coherence tomography
PCM1	pericentriolar material 1
PCyR	partial cytogenetic response
PD	pharmacodynamic(s)
PDGFRA	platelet-derived growth factor receptor, alpha polypeptide
PDGFRB	platelet-derived growth factor receptor, beta polypeptide
PET	positron emission tomography
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PP	per Protocol
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
RNA	ribonucleic acid
RPED	retinal pigmented epithelium detachment

Abbreviation	Definition
SAE	serious adverse event
SD	stable disease
SRD	serous retinal detachment
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

Pemigatinib is an inhibitor of the fibroblast growth factor receptor (FGFR) family of receptor tyrosine kinases that is proposed for the treatment of myeloid/lymphoid neoplasms with FGFR1 rearrangement. Aberrant signaling through FGFR resulting from gene amplification or mutation, chromosomal translocation, and ligand-dependent activation of the receptors has been demonstrated in multiple types of human cancers. Fibroblast growth factor receptor signaling contributes to the development of malignancies by promoting tumor cell proliferation, survival, migration, and angiogenesis. Incyte is proposing to study pemigatinib for the treatment of myeloid/lymphoid neoplasms with FGFR1 rearrangement. Refer to the Investigator's Brochure (IB) for additional background information on pemigatinib.

1.1.1. Fibroblast Growth Factor Receptor Inhibition in Oncology

The mammalian FGFR family is composed of 4 highly conserved receptors (FGFR1, FGFR2, FGFR3, and FGFR4) that have an extracellular ligand-binding domain, a single transmembrane domain, and an intracellular tyrosine kinase domain. There are 22 known FGF ligands, but only 18 of them bind to FGFRs, leading to receptor dimerization, activation of the kinase domain, and transphosphorylation of the receptors (Ornitz and Itoh 2015). Subsequent signal transduction occurs through phosphorylation of substrate proteins, such as FGFR substrate 2, which leads to activation of the RAS-mitogen–activated protein kinase and phosphoinositide 3-kinase–protein kinase B pathways, and phospholipase Cγ, which activates the protein kinase C pathway. In some cellular contexts, signal transducer and activator of transcription proteins are also activated by FGFRs. Signaling through the FGF-FGFR pathway is tightly controlled through feedback regulation. Mitogen-activated protein kinase phosphatases and Sprouty proteins are upregulated upon FGFR stimulation and antagonize FGF-dependent activation of extracellular signal-regulated kinases. In many cases, FGFR pathway activation promotes cell proliferation, survival, and migration; however, cellular context plays an important role, and in certain tissues, FGFR signaling results in growth arrest and cellular differentiation (Dailey et al 2005).

In adults, FGF-FGFR signaling is involved in angiogenesis during wound healing. The hormonal FGF ligands contribute to regulation of metabolic pathways involving lipid, glucose, phosphate, and vitamin D (Itoh 2010). Genetic defects in the FGF23-signaling pathway lead to disordered phosphate metabolism; loss of function mutations in FGF23 or its signaling result in retention of phosphate and tissue mineralization, while gain of function mutations in the FGF23 pathway manifests as hypophosphatemic Rickets syndrome (Farrow and White 2010).

There is strong genetic and functional evidence that dysregulation of FGFR can lead to the establishment and progression of cancer. Genetic alterations in FGFR1, FGFR2, and FGFR3 have been described in many tumor types (Knights and Cook 2010, Turner and Grose 2010). These include activating mutations, translocations, and gene amplification resulting in ligand-independent, constitutive activation of the receptors or aberrant ligand-dependent signaling through FGFRs.

Dysregulation of FGF ligands has also been reported in many human cancers. Preclinical studies have shown that high levels of FGF ligands, such as FGF2, promote cancer cell resistance to radiation, chemotherapeutics, and targeted cancer drugs (Fuks et al 1994, Pardo et al 2002,

Terai et al 2013). Clinically, detection of high levels of FGF2 in tumors is associated with poorer outcome in several tumor types, including non–small cell lung cancer (Donnem et al 2009, Rades et al 2012).

A substantial body of evidence supports that genetically activated FGFR pathway sensitizes FGFR-altered cancer cells to knockdown or inhibition of these receptors (Kunii et al 2008, Qing et al 2009, Weiss et al 2010, Lamont et al 2011). A large screen of more than 500 tumor cell lines with a selective FGFR inhibitor demonstrated that only a small percentage (5.9%) of all cells are sensitive to FGFR inhibition, and growth-suppressed cell lines were highly enriched for FGFR alterations (Guagnano et al 2012). These results demonstrate that FGFR inhibitors are active in a targeted manner against cancers with activated FGFR pathway. An implication of these data is that selection based on molecular-, genetic-, or protein-based diagnostic tests for specific FGFR alterations in tumors may be important for identifying patients most likely to benefit from an FGFR inhibitor.

Fibroblast growth factor receptor selective inhibitors like pemigatinib are being actively developed to target cancers with activated FGFR pathway. Fibroblast growth factor receptor inhibitors have been approved for the treatment of FGFR-altered, locally advanced or metastatic cholangiocarcinoma and urothelial carcinoma (Ellinghaus et al 2022).

An on-target pharmacologic effect of FGFR inhibition in clinical studies is hyperphosphatemia (HP). In the INCB 54828-101 study, at the recommended Phase 2 dose of 13.5 mg, 83.8% of subjects developed HP (serum phosphate > 5.5 mg/mL). Hyperphosphatemia has been managed with diet modifications and phosphate binders.

Pemigatinib is a potent selective inhibitor of FGFR1, FGFR2, and FGFR3 and is proposed for the treatment of subjects with myeloid/lymphoid neoplasms with FGFR1 rearrangement based on the presence of an 8p11 translocation.

1.1.2. Myeloid/Lymphoid Neoplasms With FGFR1 Rearrangement

Patients with myeloproliferative neoplasms (MPNs) who do not fit into any one of the easily definable categories like chronic myeloid leukemia or polycythemia vera can prove to be challenging for the physician to classify them. However, looking at the genomic sequencing of these MPN patients makes classifying them a little easier according to the 2016 WHO classification of myeloid neoplasms and acute leukemia (Arber et al 2016).

Before 2008, patients with MPN were diagnosed based on other characteristics. For example, patients with eosinophilia were diagnosed with eosinophilia myeloproliferative syndrome (EMS). Eosinophilia myeloproliferative syndrome was first identified in 1968 as "hypereosinophilic syndrome" (Park et al 2008), with the eosinophil levels playing a large part in the identification of this syndrome. Since then, physicians and researchers have identified additional characteristics similar in this syndrome, including the following: 1) MPN associated with eosinophilia; 2) lymphadenopathy, usually involved by T-lymphoblastic lymphoma/leukemia; 3) frequent progression to acute myeloid leukemia; and 4) reciprocal translocations involving chromosome 8p11 (Jackson et al 2010).

Numerous changes have occurred in the classification of EMS over the past decade. Because of this in addition to the lack of genomic sequencing until recently, the incidence of this population is difficult to determine with any kind of certainty. From the literature, MPN with FGFR1

rearrangement is clearly a very rare indication (Jackson et al 2010) with fewer than 100 cases noted in any 1 article. Most references cite a single patient response. In 2008, the new World Health Organization Classification System for Myeloproliferative Neoplasms was released. Subjects with EMS could be classified as "MPN, unclassifiable" or "Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1 or with PCM1-JAK2" with a subclassification of myeloid/lymphoid neoplasms with FGFR1 rearrangement (Tefferi et al 2009, Arber et al 2016). In the end, while it is a disease that has had many names, it is an aggressive neoplasm that is associated with chromosomal translocations involving FGFR1 (Jackson et al 2010).

In addition to changes in classification and uncertainty around incidence, the response criteria for myeloid/lymphoid neoplasms with FGFR1 rearrangement have not been established. The proposed criteria for this study have been developed based on revision of recently published criteria for myelodysplastic syndrome/MPNs (Savona et al 2015). The criteria take into account clinical, morphological, and genetic aspects of the disease for complete response (CR), partial response (PR), and cytogenetic remission, respectively, as well as potential indicators of clinical benefit. In addition, modified Lugano criteria (Cheson et al 2014) will be used to assess response in subjects' EMD, if applicable (Appendix E).

1.2. Study Rationale

Cancer has several common characteristics that can be observed across numerous tumor types. One common characteristic is the uncontrolled growth and survival of cells and their ability to become invasive throughout the body. Fibroblast growth factor signaling produces mitogenic, anti-apoptotic, and angiogenic responses in cells, which leads to a deregulated state. Evidence from several *in vitro* and *in vivo* tumor models has established the FGFs and FGFRs as oncogenes, and their expression has been found in numerous solid tumors or hematological malignancies. Several genetic alterations have been shown to generate overexpression of the FGF receptor, produce a receptor that is constitutively active, or lead it to a state where there is reduced dependence on ligand binding for activation (Knights and Cook 2010).

Tyrosine kinases are an especially important target in cancer therapy as they have a key role in growth factor signaling. Several tyrosine kinase inhibitors have been shown to be effective antitumor agents and have been approved in multiple oncology indications (Arora and Scholar 2005). Pemigatinib is a potent inhibitor of the kinase activity of FGFR1, FGFR2, and FGFR3 and has been shown to inhibit growth in several tumor models.

In the Phase 1 study (INCB 54828-101), several subjects were treated at dose levels ranging from 1 to 20 mg once daily (QD) for 2 weeks followed by 1 week off as well as continuous administration (no planned dose hold) in 21-day cycles. The maximum tolerated dose was not established. One subject with MPN FGFR1 8p11, treated with pemigatinib at 9 mg, 2 weeks on/1 week off, experienced a complete cytogenetic and morphological response with hematological improvement.

The Phase 2 starting dose has been established at 13.5 mg QD following the 2-weeks-on/ 1-week-off regimen. This dose was recommended based on safety, pharmacokinetics (PK), and preliminary signals of clinical benefit. With Protocol Amendment 3, a continuous administration regimen was introduced with a starting dose of 13.5 mg. This dose and regimen is considered

tolerable based on PK and safety data from study INCB 54828-101 (Subbiah et al 2022). The safety data for both the intermittent and continuous regimens are outlined in Section 1.3.2.

1.3. Potential Risks of the Treatment Regimen

1.3.1. Potential Risks of Pemigatinib Based on Preclinical Safety

The most prominent findings following repeat-dose exposure to pemigatinib in both rats and monkeys were HP, physeal dysplasia, and soft tissue mineralization. Mineralization was observed in numerous tissues, including the kidney, stomach, arteries (gastric and pulmonary), ovaries (monkey only), and eyes (cornea; rat only). Soft tissue mineralization was not reversible, while physeal and cartilage findings were reversible.

Hyperphosphatemia, physeal dysplasia, and soft tissue mineralization have been reported in rodents and large animals following administration of selective FGFR inhibitors (Brown et al 2005, Brown 2010, Wöhrle et al 2011, Yanochko et al 2013). These observations can be explained by the pharmacological action of FGFR inhibition. Fibroblast growth factor 23 (FGF-23)–mediated signaling negatively affects renal vitamin D biosynthesis by transcriptional repression of cytochrome P450 (CYP) 27B1, which catalyzes the production of the biologically active vitamin D metabolite 1,25(OH)2D3, and by induction of CYP24A1, which converts 1,25(OH)2D3 into a metabolite that is less biologically active. Additionally, it has been published that FGF-23 suppresses renal phosphate reabsorption by decreasing the expression of the sodium-phosphate cotransporters NPT2A and NPT2C in the brush-border membrane of proximal tubule epithelial cells (Baum et al 2005, Shimada et al 2001, Shimada et al 2004a, Shimada et al 2004b). Wöhrle et al (2011) demonstrated that FGFR inhibition by oral administration of PD176067 counteracts the biologic activity of FGF-23 in the kidney, leading to HP and hypervitaminosis D.

In rats, the mineralization was similar in distribution and morphology to that occasionally observed in normal animals; thus, it is likely that the increased incidence of mineralization in various tissues at these doses represents a test article–related exacerbation of a spontaneously occurring condition. While soft tissue mineralization was not reversible during a 28-day recovery period, there was also no evidence of progression or worsening of this effect. Soft tissue mineralization in monkeys was observed only at 3 mg/kg per day in the 10-day range-finding study and was not assessed for reversibility. No evidence of mineralization was found at the doses tested in the 28-day study in monkeys.

Moderate lens opacities (capsule, posterior) in 1 male monkey at 0.33 mg/kg per day and 1 male monkey at 1 mg/kg per day and slight attenuation of retinal vessels in 1 female monkey at 1 mg/kg per day were observed at the end of treatment (EOT) period of the 28-day GLP study. These findings were not present during the pretest period, and thus a relationship to pemigatinib cannot be dismissed. However, lens opacities are occasionally observed in normal cynomolgus monkeys of similar age and origin according to the testing facility historical control data. Persistence of lens opacity in 1 animal at the end of recovery period suggests that this finding is not reversible.

Fully reversible mild-to-moderate elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were noted at the EOT period in the 28-day monkey study at doses ≥ 0.33 mg/kg per day; these changes were not associated with changes in other hepatobiliary

parameters or microscopic changes in the liver. These changes may be related to FGFR4 inhibition, which is known to result in increases in liver function tests without histological correlates (Pai et al 2012).

In the 28-day study in rats, no severe toxicity was observed; the no-observed-adverse-effect level (NOAEL) was determined as 1.05 mg/kg per day (6.3 mg/m^2 per day), the highest dose tested. The human equivalent dose (HED) associated with 1.05 mg/kg per day based on standard body surface area conversion is 10.1 mg. The AUC associated with this dose was 3.1 µM·h (0.125 µM·h unbound). In the 28-day monkey study, no severe toxicity was observed. The NOAEL was considered to be 1 mg/kg per day (12 mg/m^2 per day), the highest dose tested. The HED associated with 1 mg/kg per day based on standard body surface area conversion is 19.2 mg. The AUC associated with this dose was 1.7 µM·h (0.148 µM·h unbound). The dose of 13.5 mg QD for this study is expected to provide an AUC of approximately 0.63 µM·h (~0.06 µM·h, unbound) which is approximately 20- to 25-fold lower (based on unbound) than exposures associated with the NOAELs in the toxicology studies.

More information can be found in the IB.

1.3.2. Potential Risks of Pemigatinib Based on Clinical Safety

As of 16 APR 2023, a total of 990 subjects have been treated with at least 1 dose of pemigatinib (133 subjects received pemigatinib in clinical pharmacology studies, and 857 subjects with hematologic malignancies received pemigatinib as monotherapy or combination therapy).

Treatment-emergent AE data from 7 open-label, nonrandomized studies of pemigatinib monotherapy (Studies INCB 54828-101 [monotherapy arm], -102, -201, -202, -207, -209, and -210), as well as monotherapy data from the rollover study INCB 54828-801, were combined and are summarized in Table 1. In the total population, the most frequently reported TEAE (≥ 50% of subjects) was HP (448 subjects [61.2%]).

Table 1: Summary of Treatment-Emergent Adverse Events by Reference Safety Information Category Occurring in ≥ 10% of Total Subjects Receiving Pemigatinib Monotherapy for Advanced Malignancies

MedDRA Preferred Term, n (%)	Intermittent Dosing (N = 438)	Continuous Dosing (N = 294)	Total[a] (N = 732)
Hyperphosphataemia	230 (52.5)	218 (74.1)	448 (61.2)
Diarrhoea	190 (43.4)	116 (39.5)	306 (41.8)
Stomatitis	151 (34.5)	151 (51.4)	302 (41.3)
Alopecia	179 (40.9)	116 (39.5)	295 (40.3)
Dry mouth	132 (30.1)	108 (36.7)	240 (32.8)
Fatigue	156 (35.6)	83 (28.2)	239 (32.7)
Constipation	139 (31.7)	96 (32.7)	235 (32.1)
Nausea	134 (30.6)	79 (26.9)	213 (29.1)
Decreased appetite	128 (29.2)	84 (28.6)	212 (29.0)
Dysgeusia	120 (27.4)	92 (31.3)	212 (29.0)
Dry eye	88 (20.1)	63 (21.4)	151 (20.6)
Vomiting	91 (20.8)	54 (18.4)	145 (19.8)
Arthralgia	85 (19.4)	56 (19.0)	141 (19.3)
Anaemia	71 (16.2)	58 (19.7)	129 (17.6)
Dry skin	73 (16.7)	53 (18.0)	126 (17.2)
Asthenia	64 (14.6)	61 (20.7)	125 (17.1)
Abdominal pain	80 (18.3)	39 (13.3)	119 (16.3)
Urinary tract infection	71 (16.2)	48 (16.3)	119 (16.3)
Blood creatinine increased	54 (12.3)	58 (19.7)	112 (15.3)
Palmar-plantar erythrodysaesthesia syndrome	40 (9.1)	72 (24.5)	112 (15.3)
Back pain	71 (16.2)	39 (13.3)	110 (15.0)
Weight decreased	61 (13.9)	44 (15.0)	105 (14.3)
Pain in extremity	54 (12.3)	40 (13.6)	94 (12.8)
Hypophosphataemia	67 (15.3)	24 (8.2)	91 (12.4)
Hypercalcaemia	51 (11.6)	32 (10.9)	83 (11.3)
Epistaxis	47 (10.7)	33 (11.2)	80 (10.9)
Oedema peripheral	44 (10.0)	34 (11.6)	78 (10.7)
Pyrexia	51 (11.6)	26 (8.8)	77 (10.5)
Onycholysis	37 (8.4)	37 (12.6)	74 (10.1)
Hyponatraemia	41 (9.4)	32 (10.9)	73 (10.0)
Nail discolouration	33 (7.5)	40 (13.6)	73 (10.0)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
Note 1: Subjects were counted only once under each MedDRA preferred term.
Note 2: MedDRA preferred terms were presented in descending order of frequency using the total column.
Note 3: For subjects who transitioned to the rollover study (INCB 54828-801), the AEs captured in the rollover study were linked back to the AEs collected in the parent studies.
[a] Includes subjects from Studies INCB 54828-101 (Part 1 and 2), -102, -201, -202, -207, -209, and -210.

In the total population, 315 subjects (43.0%) who received monotherapy had a serious TEAE. In subjects who received intermittent dosing, 191 subjects (43.6%) had a serious TEAE; in subjects who received continuous dosing, 124 subjects (42.2%) had a serious TEAE. In the total population, the most frequent serious TEAEs (≥ 2.5% of subjects) were urinary tract infection (23 subjects [3.1%]), pneumonia (20 subjects [2.7%]), and abdominal pain (18 subjects [2.5%]). In the total population, the most frequent serious TEAEs (> 1 subject) that were considered related to pemigatinib by the investigator were hyponatremia (4 subjects [0.5%]); anemia and fatigue (3 subjects [0.4%] each); and diarrhea, hypercalcemia, and nausea (2 subjects [0.3%] each).

As of 16 APR 2023, in this study, 47 participants with hematologic malignancies received pemigatinib 13.5 mg QD on an intermittent and/or continuous schedule. All 47 participants (100%) had at least 1 TEAE. The most frequently occurring TEAEs (≥ 50% of participants) were HP (35 participants [74.5%]), diarrhea (29 participants [61.7%]), and alopecia (27 participants [57.4%]). A total of 28 participants (59.6%) had serious TEAEs. The only serious TEAEs reported in more than 1 participant were acute kidney injury (3 participants [6.4%]) and atrioventricular block complete and urinary tract infection (2 participants [4.3%] each). The following serious TEAEs were considered related to pemigatinib by the investigator and occurred in 1 participant (2.1%) each: alopecia, acute kidney injury, calciphylaxis, corneal abscess, erysipelas, HP, hypertransaminasemia, osteomyelitis, pain, pneumonia pseudomonal, and syncope. Four participants (8.5%) had a fatal TEAE. The fatal TEAEs were acute kidney injury, intervertebral discitis, malignant neoplasm progression, and multiple organ dysfunction syndrome (1 participant [2.1%] each). Six participants (12.8%) had a TEAE leading to pemigatinib discontinuation: blood ALP increased, cardiac failure, calciphylaxis, keratitis, lacrimation increased, and multiple organ dysfunction syndrome (1 participant [2.1%] each).

More information on the safety of pemigatinib can be found in the IB.

1.3.2.1. Pharmacokinetic/Pharmacodynamic Summary

In Study INCB 54828-101, pemigatinib exhibited linear PK over the dose range (1 to 20 mg) evaluated. Pemigatinib is rapidly absorbed, attaining peak plasma concentrations in approximately 1 to 2 hours after oral administration, and the mean $t_{½}$ is 18.8 hours. At the 13.5 mg QD dose, the average steady-state C_{max} value is 256 nM, and the average AUC value is 2980 nM·h; mean steady-state oral clearance of pemigatinib is low (12.5 L/h), and apparent steady-state volume of distribution is moderate (293 L). The PK parameters for continuous administration are similar to those for intermittent dosing.

The projected average inhibition of FGFR2 based on PK and in vitro potency of pemigatinib ranged from 41% at 1 mg to 97% at 20 mg. Consistent with this projection, the observed inhibition of pFGFR2 in KATOIII cells spiked to ex vivo whole blood samples collected from subjects at trough was 82% after the 13.5 mg QD dose and 64% after the 9 mg QD dose. The steady-state plasma concentrations of pemigatinib after 13.5 mg QD dose that exceeded in vivo IC_{50} over a 24-hour dosing period is showed in Figure 1. The magnitude and frequency of HP was also dose-dependent. In the 9 mg cohort, 1 of 3 subjects developed HP in Part 1; 3 additional subjects were enrolled at 9 mg in Part 2. Of a total of 6 subjects administered 9 mg, 4 experienced HP; in the 13.5 mg cohort, all 6 subjects developed HP, which was managed with

a low-phosphate diet and introduction of phosphate binders. Furthermore, the increase in serum phosphorus observed after treatment with pemigatinib was exposure-dependent (see Figure 2).

Figure 1: Pemigatinib Plasma Concentrations (Mean ± SE) at Steady State After 13.5 mg QD Oral Doses of Pemigatinib

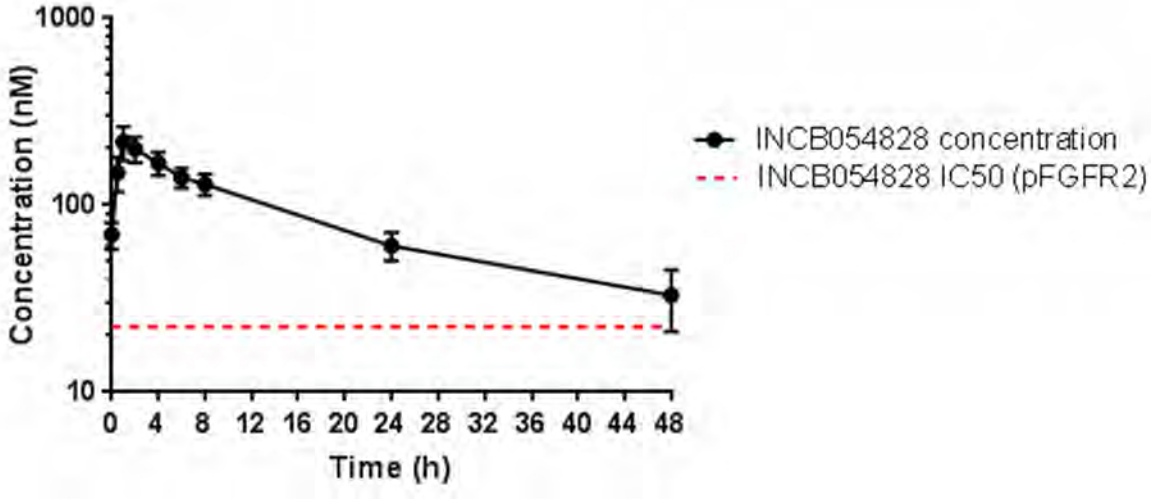
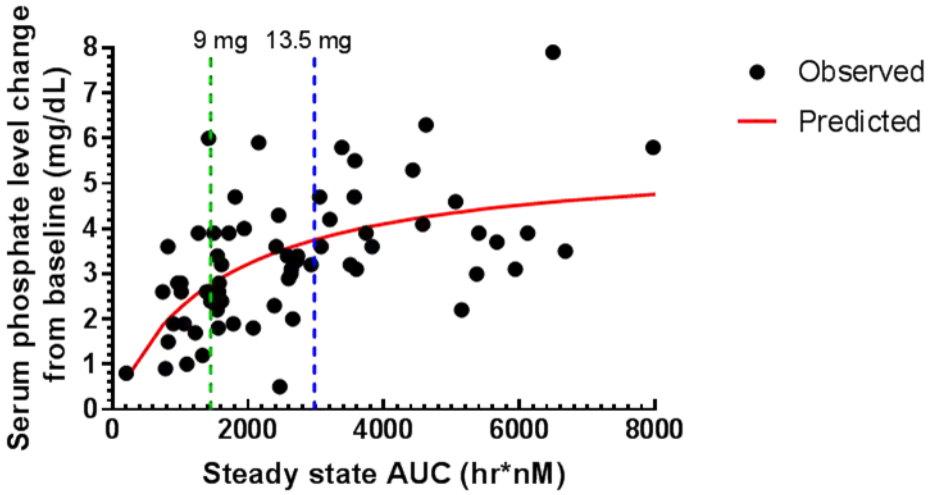


Figure 2: Serum Phosphate Versus Exposure



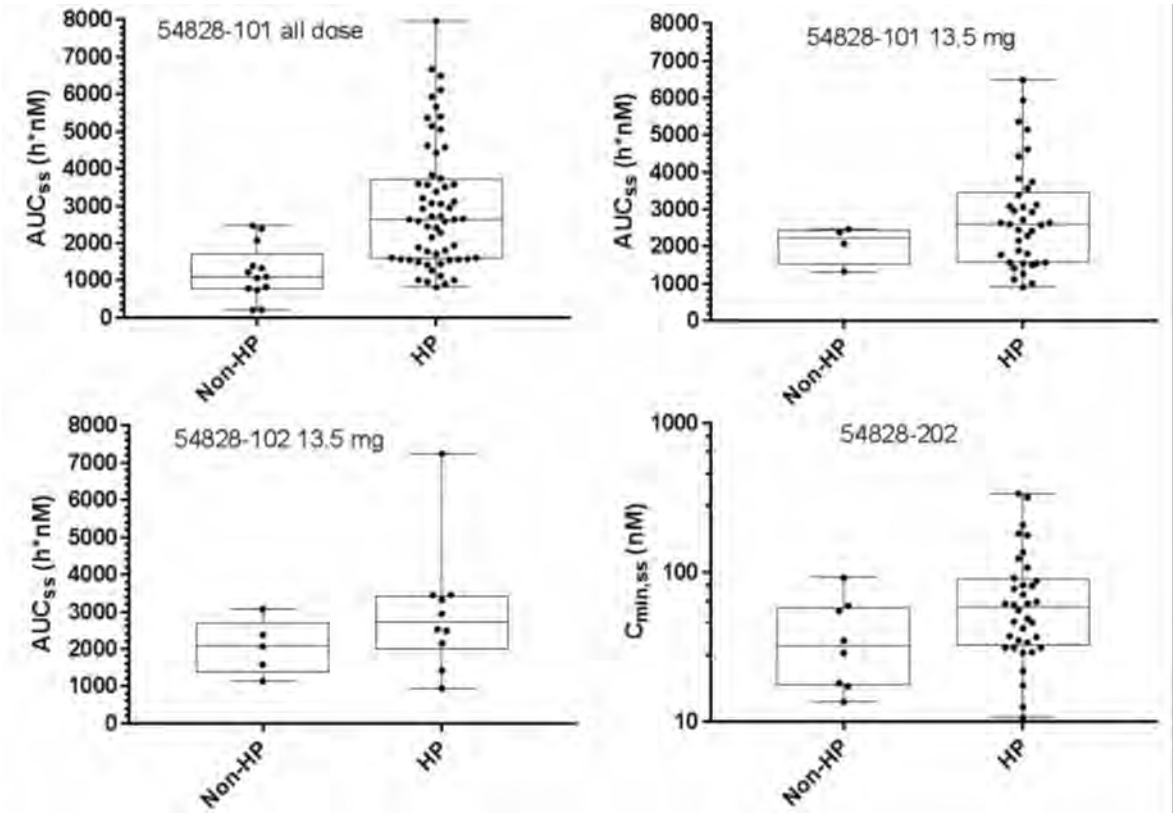
Therefore, based on a manageable safety profile and a favorable PK/PD profile, the targeted starting dose for Phase 2 is 13.5 mg. This dose is being tested in 2 additional Phase 2 protocols in subjects with urothelial cancer (INCB 54828-201) and cholangiocarcinoma (INCB 54828-202) previously submitted to IND 124,358 with the Division of Oncology Products 1.

In addition, PK data generated in the INCB 54828-101 study with continuous administration (9 mg and 13.5 mg) has shown concordance with the PK profile of subjects receiving interval administration for Cycle 1.

Hyperphosphatemia is an expected on-target pharmacological effect of FGFR inhibition. The incidence of hyperphosphatemia, defined as any postbaseline phosphate level exceeding 5.5 mg/dL, has been observed in the majority of subjects treated with pemigatinib (refer to the IB

for complete data). Some subjects do not achieve hyperphosphatemia, and it is estimated that the pharmacological concentration of pemigatinib in these subjects is lower (see Figure 3).

Figure 3: Comparison of Steady-State Exposures for Pemigatinib 13.5 mg QD Between Subjects With Nonhyperphosphatemia and Hyperphosphatemia



AUC_{ss} = area under the curve at steady state; $C_{min,ss}$ = minimum blood plasma concentration at steady state; HP = hyperphosphatemia.

The increase in serum phosphorus observed after treatment with pemigatinib was exposure-dependent and followed a sigmoid relationship. A population E_{max} model of pemigatinib AUC and maximal serum phosphate change from baseline was developed. For those subjects treated with pemigatinib 13.5 mg who did not develop hyperphosphatemia, AUC for pemigatinib 18 mg was estimated using a linear exposure relationship. Maximal serum phosphate change from baseline for each individual was then estimated using a population model. The maximal serum phosphate after treatment with pemigatinib 18 mg was calculated by adding the baseline of serum phosphate. The simulation suggested that the serum phosphate would increase above 5.5 mg/dL after treatment with pemigatinib 18 mg for the subjects treated with pemigatinib 13.5 mg who did not develop hyperphosphatemia.

Therefore, Protocol Amendment 4 allowed up-titration of pemigatinib to increase the dose of pemigatinib in subjects who do not achieve hyperphosphatemia when treated with 13.5 mg QD. The goal is to increase the serum concentration of pemigatinib for subjects who are assumed to have lower exposure based on a lower serum phosphate level while on treatment. See Section 5.4.4 for details.

Subjects will be monitored on an ongoing basis throughout this study as per the schedule of assessments (see Table 4 and Table 5).

1.3.3. Phototoxicity

Pemigatinib did not demonstrate phototoxic potential in preclinical studies (refer to the IB for more information). As a result, no precautions are required to protect from sun/ultraviolet light.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of pemigatinib in subjects with myeloid/lymphoid neoplasms with FGFR1 rearrangement.

2.1.2. Secondary Objectives

The secondary objective is to evaluate the safety and efficacy of pemigatinib in subjects with myeloid/lymphoid neoplasms with FGFR1 rearrangement.

2.1.3. Exploratory Objectives

[redacted]

2.2. Study Endpoints

2.2.1. Primary Endpoint

The primary endpoint of this study is the proportion of subjects who achieve CR as determined by investigator assessment according to the response criteria listed in Appendix E.

2.2.2. Secondary Endpoints

The secondary endpoints for this study are as follows:

- The proportion of subjects who achieve response, defined as a best response of CR or PR, as determined by investigator assessment according to the response criteria listed in Appendix E.
- The proportion of subjects who achieve a complete cytogenetic response (CCyR) as assessed by local analysis and investigator evaluation.
- The proportion of subjects who achieve a partial cytogenetic response (PCyR) as assessed by local analysis and investigator evaluation.
- Duration of CR, defined as the time from first assessment of CR to the earlier of disease progression or death due to any cause.

- Duration of response, defined as the time from first assessment of CR or PR to the earlier of disease progression or death due to any cause.
- Progression-free survival.
- Overall survival.
- Safety and tolerability, as assessed by evaluating the frequency, duration, and severity of AEs; through review of findings of physical examinations, changes in vital signs, and electrocardiograms (ECGs); and through clinical laboratory blood and urine sample evaluations.

2.2.3. Exploratory Endpoints

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. Men and women, aged 18 or older.
2. Documented lymphoid or myeloid neoplasm with 8p11 rearrangement known to lead to FGFR1 activation, based on standard diagnostic cytogenetic evaluation performed locally, before signing informed consent for this study.
3. Eligible subjects must
    a. Have relapsed after stem cell transplantation or after other disease modifying therapy, OR
    b. Not be current candidates for stem cell transplantation or other disease-modifying therapies.
    Note: All relapsed/refractory subjects must have evidence of either cytogenetic or hematological disease and have no evidence of residual toxicity (eg, graft-versus-host disease requiring treatment).
4. Life expectancy ≥ 12 weeks.
5. ECOG performance status 0 to 2 (see Table 8).
6. Willingness to avoid pregnancy or fathering children based on the following criteria:
    a. Woman 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 pregnancy test at screening and before the first dose on Day 1 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. A follow-up pregnancy test will be performed at EOT visit.
    Canada only: Woman of childbearing potential who has a negative pregnancy test at screening and before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (defined as the use of an effective method [barrier method] in combination with a highly effective method in preventing pregnancy [see Appendix B]) from screening through safety follow-up. Permitted methods that are highly effective (at least 99% effective) and effective in preventing pregnancy (see Appendix B) should be communicated to the subject and their understanding confirmed. A follow-up pregnancy test will be performed at EOT visit.

c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 90 days (1 sperm cycle) after the last dose. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
Canada only: Man who agrees to take appropriate precautions to avoid fathering children (defined as the use of an effective method [barrier method] in combination with a highly effective method in preventing pregnancy [see Appendix B]) from screening through 90 days (1 sperm cycle) after the last dose. Permitted methods that are highly effective (at least 99% effective) and effective in preventing pregnancy (see Appendix B) should be communicated to the subject and their understanding confirmed.

3.2. Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Treatment with other investigational study drug for any indication for any reason, or receipt of antineoplastic medications within 21 days or 5 half-lives (whichever is shorter) before first dose of study drug. For biologic therapies, last treatment must have been at least 28 days before the first dose of study drug. Subjects must have recovered (Grade ≤ 1 or at pretreatment baseline) from AEs from previously administered therapies. Hydroxyurea and low-dose steroids (equivalent to prednisone 20 mg per day) are permitted up to 24 hours before the first dose.
2. Prior receipt of a selective FGFR inhibitor.
3. Untreated brain or central nervous system (CNS) involvement that has progressed (eg, evidence of new neurological symptoms attributable to brain/CNS involvement). Subjects with treated CNS involvement are eligible if there is no evidence of progression for at least 4 weeks after CNS-directed treatment, as ascertained by clinical and cerebrospinal fluid examination, and/or brain imaging (MRI or CT scan) during the screening period, and they are on stable or decreasing dose of corticosteroids for at least 1 week.
4. Have a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma *in situ* of the cervix, or other noninvasive or indolent malignancy that has undergone potentially curative therapy.
5. Have abnormal laboratory parameters:
   a. Total bilirubin ≥ 1.5 × upper limit of normal (ULN; ≥ 2.5 × ULN if Gilbert syndrome or disease involving liver).
   b. AST and ALT > 2.5 × ULN (AST and ALT > 5 × ULN in the presence of liver involvement).
   c. Creatinine clearance ≤ 30 mL/min based on Cockcroft-Gault.
   d. Serum phosphate > institutional ULN.

e. Serum calcium outside of the institutional normal range, or serum albumin–correct calcium outside of the institutional normal range when serum albumin is outside of the institutional normal range.

6. History of human immunodeficiency virus infection.
7. Evidence of active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (defined as subjects with elevated transaminases or cirrhosis; subjects with chronic HBV/HCV infection with no cirrhosis and no elevated transaminases are allowed).
8. History or presence of an abnormal electrocardiogram (ECG) that in the investigator's opinion is clinically meaningful.
9. History of clinically significant or uncontrolled cardiac disease including unstable angina, acute myocardial infarction, New York Heart Association Class III or IV congestive heart failure within 6 months from Day 1 of study treatment administration, or uncontrolled arrhythmia. Subjects with a pacemaker or with atrial fibrillation and well-controlled rhythm for at least 1 month before the first dose will be allowed.
10. Have undergone major surgical procedure other than for diagnosis within 28 days before Cycle 1 Day 1.
11. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
12. Pregnant or nursing women or subjects expecting to conceive or father children within the projected duration of the study, starting with the screening visit through completion of safety follow-up visit (90 days from date of last dose for male subjects).
13. Concurrent antineoplastic therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, or investigational therapy). Palliative radiotherapy is allowed during screening with a minimum 2-week washout before the first dose.
14. History of calcium and phosphate hemostasis disorder or systemic mineral imbalance with ectopic calcification of soft tissues (exception: commonly observed calcifications in soft tissues, such as the skin, kidney, tendons or vessels due to injury, disease, and aging, in the absence of systemic mineral imbalance).
15. Current evidence of clinical significant corneal disorder/keratopathy (including but not limited to bullous/band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjunctivitis, etc) or retinal disorder (including but not limited to macular/retinal degeneration, diabetic retinopathy, retinal detachment, etc) as confirmed by ophthalmologic examination.
16. Current use of prohibited medication as described in Section 5.6.2.
17. Use of any potent CYP3A4 inhibitors or inducers (see Appendix C) within 14 days or 5 half-lives (whichever is shorter) before the first dose of study drug.
18. Known hypersensitivity or severe reaction to pemigatinib or excipients of pemigatinib study drug (refer to the IB).

19. Inability or unlikeliness to comply with the dose schedule and study evaluations, in the opinion of the investigator.
20. Inability to comprehend or unwillingness to sign the informed consent form (ICF).
21. Unable or unwilling to swallow pemigatinib, or significant gastrointestinal disorder(s) that could interfere with the absorption, metabolism, or excretion.
22. Any condition that would in the investigator's judgment interfere with full participation in the study, including administration of study medication and attending required study visits, pose a significant risk to the subject, or interfere with interpretation of study data.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an open-label monotherapy study of pemigatinib in subjects with myeloid/lymphoid neoplasms with FGFR1 rearrangement. Subjects will receive a QD dose of pemigatinib at 13.5 mg on a 2-week-on–therapy and 1-week-off–therapy schedule. With Protocol Amendment 3, the administration schedule was adjusted, and newly enrolled subjects will receive pemigatinib at 13.5 mg continuous administration (no planned dose hold). Subjects receiving treatment under previous versions of the Protocol may be switched to continuous administration after completing at least 3 cycles if there are no ongoing Grade 2 or higher related TEAEs. The written request to switch to continuous administration should be sent to the sponsor's medical monitor.

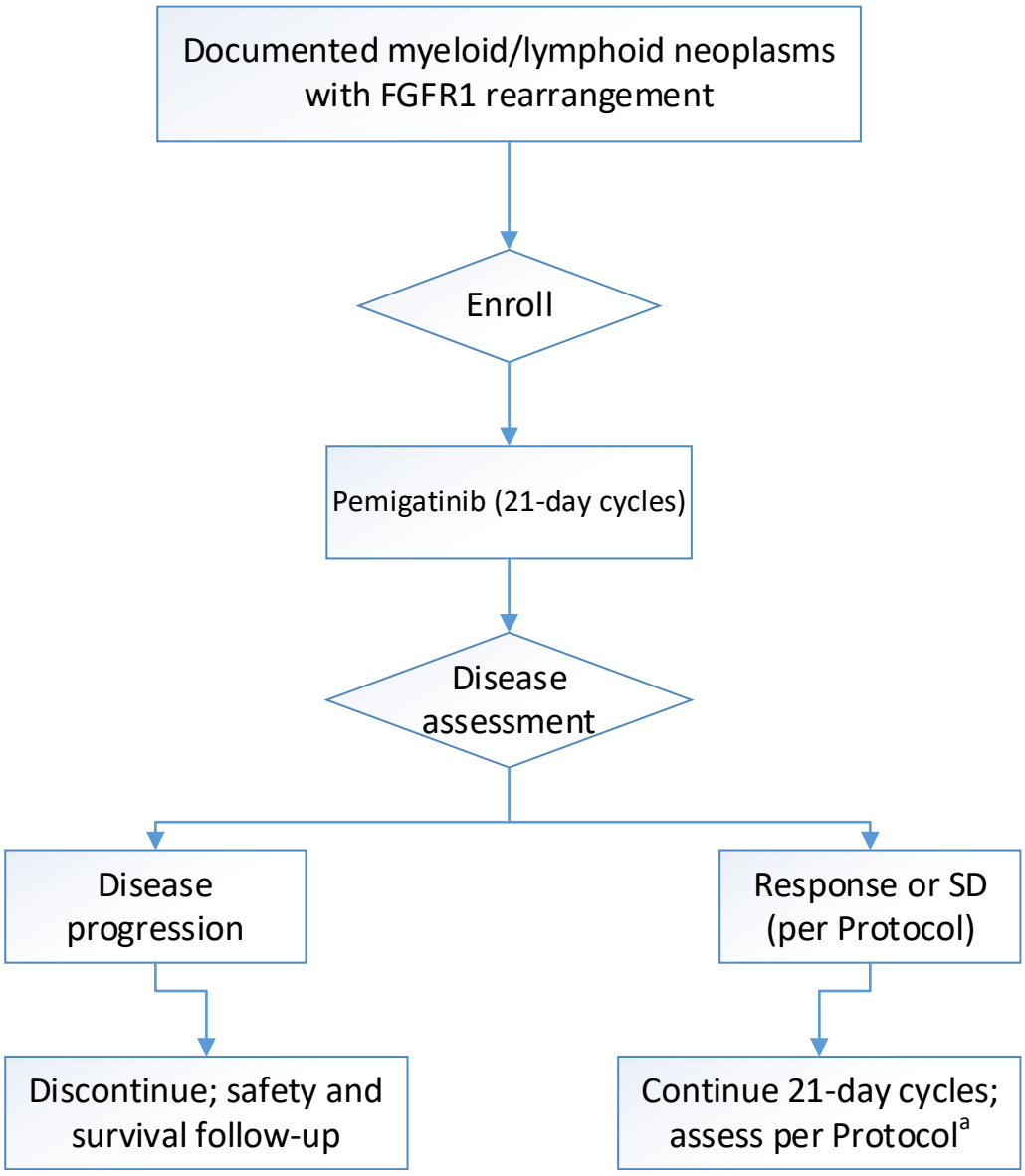
With Protocol Amendment 4, up-titration of pemigatinib was introduced. In any subject who has not had a serum phosphate level of > 5.5 mg/dL and who meet the criteria in Section 5.4.4, the investigator will increase the daily dose to 18 mg.

Full study drug administration information can be found in Section 5.2.

All potential subjects must have documentation of an 8p11 translocation known to activate FGFR1 through the site's own cytogenetics laboratory. Once documentation has been provided, the subject will then undergo screening to meet the rest of the inclusion/exclusion criteria. Once a subject has completed screening, the subject will be enrolled.

Treatment will start on Cycle 1 Day 1. Subjects will undergo regular safety assessments during treatment as well as regular efficacy assessments. Subjects will be allowed to continue administration in 21-day cycles until study treatment withdrawal criteria are met. The study design is shown in Figure 4.

Figure 4: Study Design



[a] Subjects with HSCT should continue to have peripheral blood smears, CBCs, differentials, bone marrow biopsies, bone marrow aspirates, and cytogenetics as per standard of care.

4.2. Measures Taken to Avoid Bias

This is an open-label study; no comparisons will be made between subjects or against historical controls. Measurements of safety and efficacy are objective measurements, and only comparisons to pretreatment conditions will be made.

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

Approximately 46 subjects are planned for enrollment.

4.3.2. Replacement of Subjects

Not applicable.

4.4. Duration of Treatment and Subject Participation

After signing the 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 in continuous 21-day cycles. At the point when the subject discontinues study drug (pemigatinib), the treatment period will end, and the subject will enter the follow-up period (see Section 6.4). Study participation is expected to average approximately 6 months per individual subject.

4.5. Overall Study Duration

The study begins when the first subject signs the ICF. The end of the study is expected to occur when the last subject enrolled has completed 24 months of follow-up from their first postbaseline response assessment.

If there have been ≤ 2 subjects on study for more than 8 months, then a database lock of the study may occur to allow for the analysis of the study data. Any remaining subjects may continue to receive study treatment as per the Protocol. The remaining subjects are considered to be on study until a discontinuation criterion is met and written notification is provided to the sponsor.

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/head of the study site (Japan) is to notify the institutional review board (IRB)/independent ethics committee (IEC) in writing of the study's completion or early termination, 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, if required by regulatory decision, or upon advice of the study committee. If the study is terminated prematurely, then the sponsor will notify the investigators/head of the study site (Japan), the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study. For Japan, the decision from the sponsor will be via the head of the study site(s), who will notify the investigators and the IRBs of the decision and reason for termination of the study.

5. TREATMENT

See Appendix F for COVID-19–related guidance.

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

The interactive response technology (IRT) will be contacted at the beginning of screening to obtain a subject number. 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.

Site staff will contact the IRT after screening is completed to enroll the subject and to allocate the subject to treatment assignment and obtain the initial study drug assignment. The investigator or designee will select the appropriate number of bottles of study drug from the stock that correspond to the dose provided by the IRT and dispense the study drug to the subject. All subsequent dispensing of study drug should follow this process. Refer to the IRT manual for detailed information.

If a subject is mistakenly given a bottle of study drug that is not the bottle assigned by the IRT, then the IRT help desk must be notified immediately. The reason for the misallocation of the study drug must be documented by the study site and reported to the IRB/IEC.

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

5.1.2. Randomization and Blinding

Not applicable, as this is an open-label, single arm study.

5.2. Study Drug

5.2.1. Pemigatinib

5.2.1.1. Description and Administration

Pemigatinib will be self-administered as a QD oral treatment on a 21-day cycle. Subjects will take study drug for 2 weeks continuously (14 days) followed by a 1-week (7 days) break. The starting dose will be 13.5 mg. With Protocol Amendment 3, the administration schedule was adjusted, and newly enrolled subjects will receive pemigatinib at 13.5 mg continuous administration (no planned dose hold). Subjects receiving treatment under previous versions of the Protocol may be switched to continuous administration after completing at least 3 cycles if there are no ongoing Grade 2 or higher related TEAEs. The written request to switch to continuous administration should be sent to the sponsor's medical monitor.

Based on results from the food effect cohort in Study INCB 54828-101, pemigatinib may be administered with or without food.

5.2.1.2. Supply, Packaging, and Labeling

Study drug will be supplied as 2 mg and 4.5 mg tablets. All tablet excipients comply with the requirements of the applicable compendial monographs (Ph Eur, USP-NF; refer to the IB). Pemigatinib tablets will be packaged in high-density polyethylene bottles. No preparation is required.

All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country.

5.2.1.3. Storage

Bottles of 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 Study Drug

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 the number of tablets needed at the time of administration.
- To not 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 with a full glass of water.
- If the subject vomits after taking study drug, then the subject should not take another dose.
- 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.
- If a dose of pemigatinib is missed by more than 4 hours, then that dose should be skipped, and the next scheduled dose should be administered at the usual time.

5.3. Treatment Compliance

Compliance with all study-related treatments should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with pemigatinib 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 the study drug 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.

5.4. Treatment Interruptions and Adjustments

5.4.1. Dose Modifications

Dose interruptions and modifications may occur for individual study subjects. The occurrence of toxicities (related or unrelated to study drug) will guide decisions for treatment interruptions and discontinuation for individual subjects.

5.4.2. Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the subject should continue or discontinue study treatment. For subjects who present with possible or confirmed serous retinal detachment/retinal pigmented epithelium detachment (SRD/RPED) based on optical coherence tomography (OCT), the guidelines in Table 2 should be followed. It is recommended to discuss the findings with the Incyte medical monitor before making changes to the subject's treatment.

Per CTCAE v 4.03, there is a grading for retinal detachment, however, this refers to rhegmatogenous retinal detachment (when a hole occurs in the retina) or exudative detachment (fluid accumulation due to inflammatory diseases). There is no exact CTCAE grading term for SRD/RPED secondary to FGFR inhibition (there is no hole in the macula, just fluid accumulation or detachment of retinal pigmented epithelium). Therefore, grading should be based on the CTCAE term "retinopathy."

Treatment with pemigatinib may be delayed up to 14 days to allow for resolution of toxicity. Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the case of any subject whose treatment has been delayed for more than 14 days before restarting treatment with pemigatinib.

Table 2: Guidelines for Interruption and Restarting of Study Drug

Toxicity/CTCAE Grade		Action Taken
Chemistry		
• AST and/or ALT is > 5.0 × ULN. • ALP > 5 × ULN. Note: In subjects with bone metastasis-related elevations at baseline, contact sponsor to discuss clinical management and possible dose reductions.		**Step 1:** Interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 except by approval of the medical monitor. **Step 2:** If assessed as related to study drug, restart study drug at next lower dose; monitor as clinically indicated.
Hy's law: ALT > 3.0 × ULN, ALP < 2 × ULN, and bilirubin ≥ 2.0 × ULN; no evidence of biliary obstruction or other causes that can reasonably explain the concurrent elevation.		Discontinue treatment.
Hematology		
ANC in subjects with baseline ANC > 1.0×10^9/L	ANC (< 0.5×10^9/L) ANC < 1.0×10^9/L with an oral temperature of at least 38.5°C **OR** with ≥ Grade 3 infection	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until resolved to ≤ Grade 1 or to baseline. **Step 2:** If assessed as related to study drug, restart study drug at next lower dose; monitor as clinically indicated.
Platelets in a subject with baseline platelets > 75×10^9/L	Platelet count < 25×10^9/L Platelet count 25-50 × 10^9/L and sustained (> 7 days) or associated with bleeding	
ANC in subjects with baseline ANC < 1.0×10^9/L	≥ 50% decrease from baseline ANC and not thought to be due to disease progression or concomitant medications per treating physician	**Step 1:** Evaluate underlying disease based on peripheral blood and bone marrow assessment as needed. **Step 2:** Consider dose interruption if cytopenias are NOT due to underlying disease. **Step 3:** Restart study drug at next lower dose; monitor as clinically indicated.
Platelets subjects with baseline platelet count < 75×10^9/L only	≥ 50% sustained decrease (> 7 days) from baseline platelet count and not thought to be due to disease progression or concomitant medications per treating physician	
Other toxicities, including SRD/RPED		
Any Grade 1 or Grade 2 toxicity		Continue study drug treatment and treat the toxicity; monitor as clinically indicated. For increased serum phosphate, see Section 5.4.3 for the recommended approach for HP management. Subjects who have abnormal serum phosphate or calcium levels should have their levels monitored at least twice a week.
Any Grade 3 toxicity, if clinically significant and not manageable by supportive care		**Step 1:** Interrupt study drug up to 2 weeks (14 days), until toxicity resolves to ≤ Grade 1 or to pretherapy baseline. **Step 2:** If assessed as related to study drug, restart study drug at next lower dose; monitor as clinically indicated.
Any recurrent Grade 3 toxicity after 2 dose reductions		Discontinue study drug treatment and follow-up per Protocol.
Any other Grade 4 toxicity		Discontinue study drug treatment and follow-up per Protocol.

ALP = alkaline phosphatase; ANC = absolute neutrophil count.

The sponsor recommends a maximum of 2 dose level reductions: subjects administered 13.5 mg can decrease to 9 mg, and if additional dose reduction is required, subjects can decrease to 4.5 mg. Subjects enrolled before Protocol Amendment 5 may have been reduced from 9 mg to 6 mg. The frequency of dosing (either intermittent or continuous) remains the same.

Subjects who are up-titrated to 18 mg from 13.5 mg can be reduced back down to a dose of 13.5 mg, followed by 9 mg and 4.5 mg reductions as needed.

With Protocol Amendment 5, a dose below 4.5 mg is not allowed. Subjects who were allowed doses below 4.5 mg previously should be given the option to increase their dose to 4.5 mg but may resume their lower dose if 4.5 mg cannot be tolerated.

5.4.3. Management of Hyperphosphatemia

Hyperphosphatemia is an expected on-target pharmacologic effect of FGFR inhibition. Hyperphosphatemia should be managed with diet modifications, phosphate binders and diuretics, or a dose reduction per the recommendations in Table 3.

For Japan, the phosphate binder lanthanum carbonate hydrate is recommended for the treatment of hyperphosphatemia and will be provided by the sponsor.

Table 3: Recommended Approach for Hyperphosphatemia Management

Serum Phosphate Level	Supportive Care	Guidance for Interruption/Discontinuation of Pemigatinib	Guidance for Restarting Pemigatinib
> 5.5 mg/dL and ≤ 7 mg/dL	Initiate a low-phosphate diet.	No action.	Not applicable.
> 7 mg/dL and ≤ 10 mg/dL	Initiate/continue a low-phosphate diet and initiate phosphate-binding therapy once serum phosphate level is > 7 mg/dL. Monitor serum phosphate at least twice a week and adjust the dose of binders as needed; continue to monitor serum phosphate at least twice a week until return to normal range.	If serum phosphate level continues to be > 7 mg/dL and ≤ 10 mg/dL with concomitant phosphate-binding therapy for 2 weeks, or if there is recurrence of serum phosphate level in this range, *interrupt* pemigatinib for up to 2 weeks (not including the planned dose hold per treatment cycle).	Restart at the same dose when serum phosphate is < 7 mg/dL. If serum phosphate level recurs at > 7 mg/dL, restart study drug with dose reduction.
> 10 mg/dL	Continue to maintain a low-phosphate diet, adjust phosphate-binding therapy, and start/continue phosphaturic agent. Continue to monitor serum phosphate at least twice a week until return to normal range.	If serum phosphate level is > 10 mg/dL for 1 week following phosphate-binding therapy and low phosphate diet, *interrupt* study drug. If there is recurrence of serum phosphate level in this range following 2 dose reductions, *permanently discontinue* pemigatinib.	Restart study drug at reduced dose with phosphate binders when serum phosphate is < 7 mg/dL.

5.4.4. Up-Titration

Any subject treated at 13.5 mg QD will be titrated up to 18 mg QD using their current dose regimen with approval from the medical monitor if the subject meets the following criteria:

- Has been on study drug for at least 1 cycle.
- Has been compliant with taking study drug.
- Has no ongoing Grade 2 or higher treatment-related AE.
- Has not had hyperphosphatemia, defined as a serum phosphate level of > 5.5 mg/dL.

Subjects who are titrated up to 18 mg QD will begin the next cycle at the new dose level and must agree to all Cycle 1 assessments (PK and safety assessments [hematology and blood chemistry]). Up-titration may occur no earlier than Cycle 2 Day 1, so that subjects are observed for phosphate level and AEs for at least 1 cycle.

5.4.5. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable toxicity not caused by the underlying malignancy 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.
- An AE requiring more than 2 dose reductions. Note: Reducing down to original dose following up-titration does not count toward the number of allowed dose reductions.
- Persistent AE requiring a delay of therapy for more than 21 days unless a greater delay has been approved by the sponsor.

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

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

- The subject becomes pregnant.
- Consent is withdrawn. Note: Consent withdrawn means that the subject can no longer be followed. Subjects may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- Unacceptable toxicity has occurred.

- Disease progression has been reported.
- Other antineoplastic treatment is initiated.

A subject **may** be discontinued 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 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.

5.6. Concomitant Medications

5.6.1. Restricted Medications

Pemigatinib is predominantly metabolized by CYP3A4. There is a sufficient safety margin, with doses greater than the recommended Phase 2 dose of 13.5 mg QD having been tested, and up to 20 mg QD is tolerable (refer to the IB). The expected 50% increase in exposure in subjects who concomitantly use CYP3A4 moderate inhibitors is covered by the safety margin. Therefore, the use of moderate CYP3A4 inhibitors should involve careful monitoring, especially in relation to safety, while moderate CYP3A4 inducers and potent CYP3A4 inhibitors and inducers are prohibited (see Appendix C).

Careful monitoring is required when pemigatinib is concomitantly administered with OCT2 substrates such as dofetilide and metformin.

Calcium-based phosphate binding medications should not be used due to a concern for soft tissue mineralization.

5.6.2. Prohibited Medications

The following medications and measures are prohibited:

- Concomitant administration of potent CYP3A4 inhibitors and inducers and moderate CYP3A4 inducers (see Appendix C). Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole.
- Any concomitant use of a selective FGFR inhibitor (other than the study drug).
- Investigational study drug for any indication.
- Use of any antineoplastic medications other than the study medication.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments (see Table 4), and all laboratory assessments will be performed as indicated in Table 5. Table 6 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.

See Appendix F for COVID-19–related guidance.

Table 4: Study Assessments

Procedure	Protocol Section	Screening	Treatment				EOT	Follow-Up			Notes
			Cycle 1			Cycle 2+*					
								Safety	Disease Status**	Survival	*See Section 6.2.1 for long-term treatment schedule. **Including post-transplant follow-up.
		Days -28 to -1	Day 1	Day 8 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)		EOT + 30 (+5) days	See Section 6.4.2	Every 12 (+2) weeks	
MLN w/FGFR1 rearrangement documentation	7.1	X									
Contact IRT	7.2	X	X			X*	X				*Assess for up-titration (Section 5.4.4)
Informed consent	7.1	X									
Eye examination (slit lamp, visual acuity, funduscopy with imaging, OCT)	7.5.5	X				X*	X				*Every 3 cycles starting with Cycle 3 or as clinically indicated.
Review inclusion and exclusion criteria	6.1	X	X								
Demography and medical history	7.3	X									
Prior/concomitant medications	7.4	X	X	X	X	X	X	X			
Physical examination/body weight, height	7.5.2	X*	X	X	X	X	X	X			*Comprehensive examination at screening only.
Vital signs	7.5.3	X	X	X	X	X	X	X			
12-lead ECG	7.5.4	X	X*	X*	X	X**	X	X			*Timed triplicate ECG (separated by 2-5 minutes) performed at predose, 1 hour postdose, and 2 hours postdose. **After 12 months on treatment, ECG to be done every 3 cycles or more often if clinically indicated.
ECOG status	7.7.1	X	X	X	X	X	X	X			
MPN-SAF/ EORTC QLQ-C30	7.7.2	X				X*	X				*Every 3 cycles starting with Cycle 3 for at least 12 months from the start of treatment (C1D1).
Review AEs	7.5.1	X	X	X	X	X	X	X			

Table 4: Study Assessments (Continued)

Procedure	Protocol Section	Screening	Treatment				EOT	Follow-Up			Notes
			Cycle 1			Cycle 2+*					
		Days -28 to -1	Day 1	Day 8 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)		Safety EOT + 30 (+5) days	Disease Status** See Section 6.4.2	Survival Every 12 (+2) weeks	*See Section 6.2.1 for long-term treatment schedule. **Including post-transplant follow-up.
EFFICACY ASSESSMENTS (Appendix E)											
Bone marrow examination (core biopsy and aspiration)	7.6, 7.9.4	X*				X**	X		X***		*Within 6 weeks before enrollment. **See Section 7.6 for assessment frequency. ***In subjects who do not discontinue due to progressive disease, including subjects in post-transplant follow-up.
Lymph node/EMD biopsy (optional)	7.6	X*				X*					*In subjects who present with lymphadenopathy or other EMD, biopsy is recommended at baseline and at the time of progression.
Cytogenetic analysis	7.6	X				X*	X		X**		*See Section 7.6 for assessment frequency. **In subjects who do not discontinue due to progressive disease, including subjects in post-transplant follow-up.
EMD assessment by PET-CT or CT scan	7.6	X			X*	X*	X*		X*		See Section 7.6 for assessment frequency. *If baseline assessment is positive for EMD.
Survival status	6.4.3									X	

CT = computed tomography; PET = positron emission tomography.

Table 5: Laboratory Assessments

	Protocol Section	Screening	Treatment				EOT	Safety Follow-Up 30 days from EOT (+5 days)	Notes
			Cycle 1			Cycles 2+			
			Day 1	Day 8 (± 3 Days)	Day 15 (± 3 Days)				
LOCAL LABORATORY									
Serum chemistries	7.5.6	X	X*	X	X	X**	X	X	*May be performed within 3 days of the first dose. **Assess for up-titration (Section 5.4.4).
Hematology	7.5.6	X	X*	X	X	X	X	X**	*May be performed within 3 days of the first dose. **Including subjects in post-transplant follow-up.
Lipid panel	7.5.6		X						
Endocrine	7.5.6	X	X			X	X		
Coagulation panel	7.5.6	X				X*	X		*Every 3 cycles starting with Cycle 3.
Hepatitis screening	7.5.6.2	X							
Urinalysis	7.5.6	X				X*			*Every 3 cycles starting with Cycle 3
Pregnancy test	7.5.6.1	X (Serum)	X*			X*	X*		*Urine pregnancy test allowed; Day 1 of each cycle (see Section 6.2.1 for long-term treatment details).

Table 5: Laboratory Assessments (Continued)

	Protocol Section	Screening	Treatment				EOT	Safety Follow-Up 30 days from EOT (+5 days)	Notes
			Cycle 1						
			Day 1	Day 8 (± 3 Days)	Day 15 (± 3 Days)	Cycles 2+			
CENTRAL LABORATORY									
Bone marrow (aspirate, core, and peripheral blood smear)	7.6, 7.9.4	X				X*	X		*See Table 7 for assessment frequency.
PK	7.8		X	X					Samples will be drawn at predose and 1, 2, and 4-12 hours postdose (4 samples total on each day).
Correlative plasma sample	7.9.3		X		X	X*			*C2D1, C4D1, C8D1, then at the times of scheduled bone marrow sampling (see Table 7 for assessment frequency).
Correlative whole blood sample for RNA	7.9.2		X		X	X*			*C2D1, C4D1, C8D1, then at the times of scheduled bone marrow sampling (see Table 7 for assessment frequency).
Correlative whole blood for DNA and epigenetics	7.9.2		X		X	X*			*C2D1, C4D1, C8D1, then at the times of scheduled bone marrow sampling (see Table 7 for assessment frequency).

Table 6: Laboratory Assessments: Required Analytes

<table>
<tr><th>Serum Chemistries</th><th>Hematology</th><th>Urinalysis With Microscopic Examination</th><th>Hepatitis Screening</th><th>Coagulation</th></tr>
<tr><td rowspan="3">Albumin
ALP
ALT
AST
Bicarbonate
Blood urea nitrogen
Calcium
Chloride
Creatinine
Glucose
Lactate dehydrogenase
Phosphate
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Total protein
Uric acid
Vitamin D (25-hydroxyvitamin D and 1,25-dihydroxvitamin D)</td><td rowspan="3">Complete blood count, including:
Hemoglobin
Hematocrit
Platelet count
Red blood cell count
White blood cell count

Differential count (manual preferred), including:
Basophils
Eosinophils
Lymphocytes
Monocytes
Neutrophils
Blasts
Nucleated red blood cells</td><td>Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein
Urobilinogen</td><td rowspan="2">Hepatitis B surface antigen
Hepatitis B surface antibody
Hepatitis B core antibody
HCV antibody
NOTE: If any of the above are positive, HBV-DNA, HCV-RNA may be done to assess risk of reactivation, if indicated (eg, no history of immunization).</td><td rowspan="2">PT
PTT
INR</td></tr>
<tr><th>Lipid Panel</th><th>Other</th><th>Pregnancy Testing</th></tr>
<tr><td>Total cholesterol
Triglycerides
LDL
HDL</td><td>Endocrine-parathyroid hormone</td><td>Female subjects of childbearing potential only require a serum test at screening and a urine pregnancy test before the first dose on Cycle 1 Day 1, Day 1 of each subsequent cycle, and at EOT.
Pregnancy tests (serum or urine) should be repeated if required by local regulations.</td></tr>
</table>

HDL = high-density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cell.
Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.

6.1. Screening

Screening is the interval between signing the ICF and the day that the subject is enrolled in the study (Cycle 1 Day 1). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the subject's routine clinical management (eg, blood count, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes provided that the procedure meets the Protocol-defined criteria and has been performed within the timeframe of the study (ie, within 28 days of Cycle 1 Day 1). All information associated with eligibility requirements must be entered into the appropriate eCRF pages.

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 screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before treatment assignment will be used to determine subject eligibility. Treatment should start as soon as possible, but within 3 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, after recovery from an infection). Subjects who are rescreened will receive a new subject number through IRT.

6.2. Treatment

The treatment period begins on the day that the subject receives the first dose of study drug (Cycle 1 Day 1) through the point at which the investigator determines that the subject will be permanently discontinued from study drug. Cycle 1 Day 1 must be no more than 28 days after the subject has signed the ICF and no more than 3 days after the date of enrollment. Dates for subsequent study visits will be determined based on this day and should occur within ± 3 days of the scheduled date unless delayed for safety reasons. At Cycle 1 Day 1, results from screening visit evaluations should be reviewed to determine whether the subject continues to meet the eligibility requirements, as specified in the Protocol.

6.2.1. Long-Term Treatment Visit Schedule

After completion of the Cycle 18 Day 1 (51 weeks on study treatment) visit, the frequency of study visits conducted at the investigative site may be extended to every 3 cycles (9 weeks) if the following criteria are met and the study site receives medical monitor approval:

- The subject has no ongoing ≥ Grade 3 TEAEs or ≥ Grade 2 treatment-related TEAEs.
- The subject has maintained an overall response of PR or better for at least 3 consecutive assessments.
- The subject has maintained a CCyR for at least 3 consecutive assessments.

- Women of childbearing potential must agree to have monthly pregnancy testing performed at home or at a local laboratory and must immediately notify the study site of a positive result so study medication can be held while a serum pregnancy test is performed. Urine pregnancy test kits may be provided to subjects.

In the interval between visits to the study site, sites must conduct remote/telemedicine visits with the subjects on Day 1 of each cycle (± normal visit window) to assess AEs, concomitant medications, ECOG performance status, and study medication compliance. Likewise, subjects must complete the scheduled laboratory assessments at a laboratory convenient to their homes. Data from these remote/telemedicine visits as well as the laboratory data collected will be entered into the eCRF at their respective cycle visits.

Subjects who may be eligible to switch to this long-term treatment visit schedule but have already surpassed Cycle 18 at the time of Protocol Amendment 6 may begin following this schedule in conjunction with a cycle that has the same assessments as Cycle 18 (eg, in conjunction with an eye exam), if the above criteria are satisfied.

Subjects may revert back to attending every study visit at the investigative site as needed (eg, to manage a new or worsening adverse event) but must always resume the extended investigative site visit schedule in conjunction with a cycle that has the same assessments as Cycle 18.

6.3. End of Treatment

When the subject permanently discontinues study drug, 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 days 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. Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur during this period.

If a subject is scheduled to begin a new antineoplastic therapy before the end of the 30-day safety follow-up period, then the safety follow-up visit should be performed before new antineoplastic therapy is started. Once new antineoplastic therapy has been initiated, the subject will move into the survival follow-up period.

6.4.2. Disease Status Follow-Up

Subjects who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up period and should be assessed according to the disease assessment frequency noted in Section 7.6 to monitor disease status. Every effort should be made to collect information regarding disease status until:

- The start of new antineoplastic therapy
- Disease progression or relapse
- Death
- The end of the study

6.4.2.1. Post-Transplant Follow-Up

Subjects who have a successful HSCT should be followed for disease status post-transplant as well. Data from standard-of-care transplant assessments (eg, pretransplant preparation, conditioning regimen, donor, type, GVHD, relapse, transplant-related mortality, graft failure, peripheral blood smears, CBCs, differentials, bone marrow biopsy, bone marrow aspirate, cytogenetics) will be collected from these subjects until they have withdrawn from the study.

Post-transplant subjects should return to the investigative site for bone marrow exams, hematology blood work and, if applicable, imaging studies, as noted in Section 7.6.

6.4.3. Survival Follow-Up

Once a subject has received the last dose of study drug, confirmed disease progression, or starts a new antineoplastic therapy, the subject moves into the survival follow-up period and should be contacted by telephone, email, or visit at least every 12 (+2) weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.5. End of Study

The end of the study may be designated as the timepoint when all subjects have discontinued the study or the sponsor terminates the study.

6.6. Unscheduled Visits

Unscheduled visits may occur at any time as medically warranted. Any assessments performed during those visits should be recorded in the eCRF.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

Subjects must have confirmation of 8p11 translocation to be considered for the study. This analysis should be performed before the subject is considered for the study and should be submitted with the screening request documentation.

Once documentation of FGFR1 8p11 translocation is reviewed and approved, 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.

7.2. Interactive Response Technology Procedure

The IRT will be contacted to obtain a subject ID number when a subject enters screening. Upon determining that the subject is eligible for study entry, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at each regular study visit to update the study drug supply. See the appropriate information in Section 5.1.1.

See Appendix F for COVID-19–related guidance.

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening.

7.3.2. Disease Characteristics and Treatment History

A disease-targeted medical and medication history will be collected at screening.

7.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures 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 28 days before first dose and up to 30 to 35 days after last dose of study drug 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.

See Appendix F for COVID-19–related guidance.

7.5. Safety Assessments

See Appendix F for COVID-19–related guidance.

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 Examinations

Physical examinations must be performed by a medically qualified individual such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits.

Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.2.1. Comprehensive Physical Examination

The comprehensive physical examination will include height (at screening), body weight, and assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes, as well as a brief neurological examination.

7.5.2.2. Targeted Physical Examination

The targeted physical examination will be a symptom-directed evaluation. The targeted physical examination will include body weight and assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings.

7.5.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the subject in the recumbent, semirecumbent, or sitting position after approximately 5 minutes of rest. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.4. Electrocardiograms

All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest. Triplicate ECGs will be performed on Cycle 1 Day 1 and Cycle 1 Day 8 at predose and 1 and 2 hours postdose. Note that triplicate ECGs should be performed with a 2- to 5-minute break between evaluations.

The 12-lead ECGs will be interpreted by the investigator at the site to 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. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs. As of Protocol Amendment 6, after 12 months on treatment, ECGs will be performed every 3 cycles or more often if clinically indicated.

7.5.5. Comprehensive Eye Examination

A comprehensive eye examination should be performed by a qualified ophthalmologist at screening, once every 3 cycles (± 14 days, starting at Cycle 3), at EOT, and as clinically indicated. The eye examination must include a visual acuity test, slit-lamp examination, funduscopy with digital imaging, and OCT. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist.

7.5.6. Laboratory Assessments

Each site's local laboratory will be used for eligibility and ongoing safety assessments. Chemistry, hematology, coagulation panel, lipid panel, serology, endocrine monitoring, and urinalysis testing will all be analyzed by each site's laboratory. As of Protocol Amendment 6, lipid panel will only be analyzed at Cycle 1 Day 1.

7.5.6.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening. A urine pregnancy test is allowed on Day 1 (before the first dose of study drug), Day 1 of each subsequent cycle, and at the EOT visit. Urine pregnancy tests will be conducted as outlined in Table 5, as medically indicated, or per country-specific requirement. 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.

See Section 6.2.1 for pregnancy test requirements for applicable subjects who enter into the long-term treatment schedule.

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.

7.5.6.2. Hepatitis Screening Tests

Subjects will undergo screening for hepatitis B or C through their local laboratory. If the results are positive, then subjects may be required to undergo additional testing to assess risk of reactivation if clinically indicated (eg, no history of immunization). Subjects with chronic or cleared hepatitis B or C will be allowed to enroll. Chronic is defined as subjects with no evidence of liver cirrhosis or active hepatitis (elevation of transaminases) but with positive anti-HCV antibody test or positive HCV RNA, positive HBV S antigen, or positive HBV DNA.

7.6. Efficacy Assessments

See Appendix F for COVID-19–related guidance.

Investigators will assess response to treatment by evaluation of local peripheral blood results, bone marrow pathology, cytogenetics, and imaging for EMD at the frequencies listed below and according to the response criteria listed in Appendix E. Investigative sites will also ship slides and samples to central labs as described below.

In addition, a Central Review Committee composed of hematopathologists and hematologists will be convened to conduct a retrospective review and adjudication of baseline diagnosis, baseline disease category (chronic phase without EMD, chronic phase with EMD, blast phase without EMD, blast phase with EMD, EMD only, or any additional categories as judged by the CRC), and response to treatment according to criteria specific to the baseline disease category. Details of the Committee's organization, responsibilities, and the adjudication processes can be found in the Committee Charter.

The interval schedule for the bone marrow and imaging assessments should be anchored to the start of study drug (Cycle 1 Day 1) and should not be delayed due to delays in cycle starts resulting from study drug interruption.

7.6.1. Peripheral Blood

Peripheral blood smears, CBCs, and differentials will be obtained at baseline and per schedule of assessments.

7.6.2. Bone Marrow Exams and Cytogenetics

Bone marrow examinations are an integral part of assessing subject response to treatment and will be collected according to the following parameters:

- The components of a complete bone marrow exam will consist of a core biopsy, marrow aspirate, and associated peripheral blood smear slides. Every reasonable effort should be made to perform a complete exam at each disease assessment, however instances where all exam components cannot be obtained (eg, aspirate is a dry tap or core biopsy is contraindicated) will not be considered protocol deviations.
- Bone marrow exams will be conducted according to the schedule provided in Table 7 and continue until disease progression or the completion of the disease follow-up period (Section 6.4.2).
- Subjects who successfully bridge to HSCT should continue to have bone marrow examinations and peripheral blood smears, CBCs, and differentials assessed according to local standard of care.

Table 7: Bone Marrow Exam Schedule

Study Phase	Exam Frequency
Screening (baseline)	• Obtained within 6 weeks of enrollment (Cycle 1 Day 1).
Treatment	• After 6 (± 1) weeks (just prior to Cycle 3) and then every 9 (± 1) weeks from Cycle 1 Day 1 for the first 12 months (eg, until Week 51/Cycle 18) on treatment. • After 12 months on treatment, every 18 (± 1) weeks for subjects who have not yet achieved CCyR or every 52 (± 2) weeks for subjects who have a confirmed CCyR. If progression is suspected in peripheral blood, a bone marrow biopsy and bone marrow aspirate should be conducted as an unscheduled visit as soon as possible.
Disease status follow-up	• Subjects who enter the disease status follow-up for reasons other than to bridge to transplant may continue to have disease assessments according to the schedule above. • Subjects who bridge to transplant should have bone marrow examinations and peripheral blood smears, CBCs, and differentials at 1 to 3 months and 6 months post-transplant and then as per local standard of care. Slides from these exams will be forwarded to the central pathologist for review.

Flow cytometry is not a required component of the bone marrow exam; however, if it is performed, the results should be captured in the eCRF.

Cytogenetic analysis of the bone marrow aspirate should be performed locally, and results will be recorded in the eCRF. Locally assessed cytogenetics results with fewer than 20 metaphases for examination should be repeated within 1 month if clinically feasible.

Results of local FISH analysis performed on the bone marrow aspirate samples should be recorded in the eCRF. Additionally, a separate aspirate sample will be sent for central analysis of FGFR1 fusion on chromosome 8p11 and other genetic mutations. Detailed instructions of the collection, processing, handling, storage, and shipment will be provided in a separate procedure manual at the time of study initiation. NOTE: Peripheral blood will be accepted as a substitute for bone marrow only if the marrow aspiration is a dry tap.

Molecular analysis of the bone marrow samples is not required for disease assessments but should be collected and assessed if possible; if performed locally, the results should be entered in the eCRF.

7.6.3. Extramedullary Disease

Extramedullary disease will be assessed via radiologic imaging studies and evaluation of hepatosplenomegaly on physical exam.

All subjects will have a diagnostic quality imaging study performed during screening to determine the presence of EMD (eg, lymphadenopathy, myeloid sarcoma). Due to the aggressive nature of the disease under study, extramedullary lesions are expected to be avid. As such, FDG PET-CT is the preferred method for detecting and evaluating EMD. Participating investigators who cannot perform PET scans (eg, due to country regulations, institution

capabilities, local standard of care, etc) should still evaluate subjects for EMD by diagnostic quality CT scans with contrast.

Identification and tracking of measureable EMD may more precisely assist in gauging response to treatment. As such, whenever possible, the CT component of the PET-CT scans should be of diagnostic quality and performed with contrast whenever possible.

Subjects who present with EMD at baseline will have follow-up imaging assessments at the following intervals:

- Subjects with baseline PET scans will have a repeat PET scan on Cycle 1 Day 15 (companion CT not required).
- PET-CT or CT scan with contrast in conjunction with the schedule of bone marrow examinations listed above.
- Note the same imaging modality must be used throughout the entire study.

Hepatosplenomegaly will be assessed by palpation on physical exam at baseline and per schedule of assessments.

In subjects who present with lymphadenopathy or other EMD, biopsy is recommended at baseline and at the time of progression.

7.6.4. Assessment of Disease Response

Investigators will assess subjects' response to treatment by local evaluation of peripheral blood, bone marrow pathology, and cytogenetics and imaging studies (if applicable) at the frequencies listed above and according to the response criteria listed in Appendix E.

Additionally, a central review committee composed of hematopathologists and hematologists will be convened to conduct a retrospective review and adjudication of subject's baseline disease and response to treatment. Details of the committee's organization and responsibilities can be found in the committee charter.

7.7. Performance and Quality-of-Life Assessments

See Appendix F for COVID-19–related guidance.

7.7.1. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status (Table 8) will be assessed at the visits specified in the schedule of assessments (Table 4).

Table 8: Eastern Cooperative Oncology Group Performance Status

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.

Source: Oken et al 1982.

7.7.2. Quality-of-Life Assessment

Subjects will be asked to complete the EORTC QLQ-C30 questionnaire (Aaronson et al 1993) and the MPN-SAF questionnaire (Scherber et al 2011) at regular intervals throughout the study (see Table 4) for at least 12 months from the start of treatment (Cycle 1 Day 1).

7.8. Pharmacokinetic Assessments

See Appendix F for COVID-19–related guidance.

[redacted]

7.9. Biomarker and Correlative Studies

See Appendix F for COVID-19–related guidance.

7.9.1. Timing of Assessments

Bone marrow, whole blood, and plasma samples will be collected at the visits outlined in Table 5. Additional optional specimens may be collected at any time during the study to assess changes associated with safety, efficacy, or resistance to treatment. Biomarker assessments beyond those listed may be evaluated at the discretion of the sponsor using excess biomarker or PK samples. Analyses will be conducted by Incyte Corporation (Wilmington, DE) or Incyte's designee.

For information regarding handling/shipping of specimens, refer to the Laboratory Manual for the study.

[redacted]

7.9.5. Buccal Swab

A buccal swab is no longer required, per Protocol Amendment 3.

7.10. Other Study Procedures

7.10.1. Data Collection for Survival Follow-Up

For subjects having entered the survival follow-up period of the study, the site will use continuing subject records to supply data on subsequent treatment regimens, tumor assessments (if discontinued treatment for a reason other than progression), and overall survival in the eCRF. For subjects who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, patient records, and public records/databases at intervals of no longer than 12 (+ 2) weeks. After the final primary analysis is performed, the follow-up interval for subsequent antineoplastic treatments and survival may be reduced to every 12 (+ 2) weeks (see Section 6.4).

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.

Events **meeting** the AE definition include the following:

- Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Abnormal laboratory test results constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal lab result (eg, low hemoglobin, platelet count decreased).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events **not** meeting the AE definition include the following:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition or considered to be treatment-related by the investigator.
- Efficacy endpoints as outlined in Section 2.2 will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the cancer under study. Unblinded aggregated efficacy endpoint events and safety data will be monitored to ensure the safety of the subjects in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Incyte Pharmacovigilance as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing informed consent. If present before entering the study, the condition should be captured as medical history.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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 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; minimal, 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 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).

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, that 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.

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. A dose modification for the laboratory abnormality may be required (see Section 5.4) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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 on appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.
- May lead to disability (for Japan)
  - Exposure to a risk of dysfunction to the extent that interferes with daily life when the adverse drug reaction occurred. It does not mean that the adverse drug reaction may cause disability if the reaction was more severe.

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 the study treatment.

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.

For Japan, the SAE information must also be reported immediately to the head of the study site.

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 to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions 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. For Japan, suspected expected deaths and life-threatening events will also be reported to the Pharmaceuticals and Medical Devices Agency (PMDA) as per local regulatory requirements.

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 followed in order to ensure subject safety:

- The study drug must be discontinued immediately (female subjects only; see Section 5.4.2 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 IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. 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

No independent Data Monitoring Committee is planned for this study. A study committee may be established and include the investigators or designees, the sponsor representatives (eg, medical monitor), and, when appropriate, ad hoc experts.

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 subjects, 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 their 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, they will return a copy of the product complaint communication with the product.

For Japan, complaints associated with unapproved medical devices will be reported to the sponsor with a Medical Device Defect Report Form, and the sponsor will report medical device defects to the PMDA as per local regulatory requirements.

9. STATISTICS

9.1. Study Populations

The efficacy evaluable population includes all subjects who received at least 1 dose of study drug.

The per Protocol (PP) population includes all efficacy evaluable subjects who were compliant with the Protocol.

The safety population includes all enrolled subjects who received at least 1 dose of study drug.

9.2. Selection of Sample Size

Approximately 46 subjects are planned for the final analysis of the primary endpoint of overall CR rate. With the assumed rates of 35% for the intervention, a sample size of approximately 46 subjects would provide > 80% probability to have a 95% confidence interval with lower limit of > 15% assuming 10% lost to follow-up.

9.3. Level of Significance

The level of significance for the primary endpoint is 1-sided 5%.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Analyses

The primary endpoint of this study is the proportion of subjects who achieved a BOR of CR as determined by investigator assessment according to the response criteria for myeloid/lymphoid neoplasms with FGFR1 rearrangement (see Appendix E). This analysis will be based on the efficacy evaluable population. Subjects who do not have sufficient baseline or on-study response assessment information to be adequately assessed for response status will be included in the denominators in the calculation of overall response rate. The 95% CI for the proportion of subjects with CR will be estimated using the Clopper-Pearson method.

The proportion of subjects who achieved a BOR of CR will also be analyzed based on the PP population as a sensitivity analysis.

9.4.1.2. Secondary Efficacy Analyses

Secondary efficacy analyses will be conducted for the efficacy evaluable population.

The proportion of subjects who achieve response, defined as BOR of CR or PR, as determined by investigator assessment according to the response criteria listed in Appendix E, will be estimated with its 95% CI.

The proportion of subjects who achieve BOR of CCyR as assessed by local analysis and investigator evaluation will be estimated with its 95% CI.

The proportion of subjects who achieve BOR of PCyR as assessed by local analysis and investigator evaluation will be estimated with its 95% confidence interval.

Duration of CR, defined as the time from first assessment of CR to the earlier of disease progression or death due to any cause. Subjects without disease progression or death at the time of analysis will be censored at the date of last response assessment before the cutoff date. Duration of CR will be analyzed by the Kaplan-Meier method.

Duration of response, defined as the time from first assessment of CR or PR to the earlier of disease progression or death due to any cause. Subjects without disease progression or death at the time of analysis will be censored at the date of last response assessment before the cutoff date. Duration of response will be analyzed by the Kaplan-Meier method.

Progression-free survival is defined as the time from the first date of taking study drug until the date of disease progression, as measured by response criteria or until death due to any cause, whichever is earlier. Subjects who are still alive without experiencing disease progression at the time of analysis will be censored at the date of the last response assessment before the cut-off date. Progression-free survival data will be analyzed by the Kaplan-Meier method.

Overall survival is defined as the time from the first day of taking study drug until death due to any cause. Subjects without death observed at the time of the analysis will be censored at last date known to be alive. Overall survival will be analyzed by the Kaplan-Meier method.

9.4.1.3. Other Efficacy Analysis

Myeloproliferative Neoplasm Symptom Assessment Form and EORTC QLQ-30 measurements and change from baseline to each visit where MPN-SAF or EORTC QLQ-30 is measured will be summarized descriptively.

The number of subjects with SD who achieve CHR, marrow response, or clinical benefit, as determined by as determined by investigator assessment according to the response criteria in Appendix E will be summarized.

9.4.2. Safety Analyses

9.4.2.1. Adverse Events

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after the 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 (NCI 2010) using Grades 1 through 4.

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.

Subjects taking pemigatinib may develop HP, which is a known effect of selective FGFR inhibitors. The number and percentage of subjects with at least 1 event of HP will be tabulated.

9.4.2.2. 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 Grades 1 through 4 using CTCAE v4.03. The following summaries will be produced for the laboratory data:

- Number and percentage of subjects with worst postbaseline CTCAE grade (regardless of baseline value). Each subject will be counted only for the worst grade observed postbaseline.
- Shift tables from baseline to the worst postbaseline value using CTCAE grade.
- For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value using the low/normal/high classifications based on laboratory reference ranges.

9.4.2.3. 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 9), 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 9: 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

9.4.2.4. 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 10). Subjects exhibiting clinically notable ECG abnormalities will be listed.

Table 10: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 470 ms	< 295 ms
PR	> 220 ms	< 75 ms
QRS	> 120 ms	< 50 ms
QT	> 500 ms	< 300 ms
RR	> 1330 ms	< 600 ms

QTcF = Fridericia correction.

[redacted]

9.5. Analyses for the Data Monitoring Committee

Not applicable.

9.6. Interim Analysis

No interim analysis is planned.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Investigator Responsibilities

- The Protocol, Protocol Amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC and health authorities before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both health authorities and the IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- 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 during the retention period 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.

- For Japan, the record retainer (delegated by the head of the study site) will retain the Japan-Good Clinical Practice (J-GCP)–defined essential documentation at this site until the regulatory approval of the study drug or at least 3 years after the discontinuation or completion of the study conduct, whichever is later. If the sponsor requires retention of these documents for a longer period of time, the duration and method of retention will be decided upon through discussion between the sponsor and the study site. It is the responsibility of the sponsor to inform the head of the study site as to when the documents no longer need to be retained.

10.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor before the end of the study. As part of their responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

10.2. Accountability, Handling, and Disposal of Study Drug

See Appendix F for COVID-19–related guidance.

The investigator and investigational drug storage manager (for Japan) are 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, investigational drug storage manager (for Japan), 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, investigational drug storage manager (for Japan), or designee by subjects.

The investigational product must be used only in accordance with the Protocol. The investigator or investigational drug storage manager (for Japan) 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, investigational drug storage manager (for Japan), 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,

investigational drug storage manager (for Japan), 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.

Further guidance and information for the final disposition of unused study treatments are provided in Japanese-specific note of the Pharmacy Manual.

10.3. Data Management

Data management will be performed in a validated electronic data capture (EDC) system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each subject.

The site will be provided with eCRF completion guidelines for instructions on data entry in 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. Other data outside the EDC system required in the study conduct of the Protocol, such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and as designated by the sponsor, will have their own data flow management plans, study charters, or biomarker plans, as applicable.

The sponsor (or designee) will be responsible for the following:

- Managing the integrity of the data and the quality of the conduct of the study, such as ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved Protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Managing and reconciling the data generated and/or collected, including documents and results such as laboratory or imaging data analyzed centrally by a designated vendor of the sponsor.

The investigator will be responsible for the following:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, biomarker data, photographs, diary data) or as otherwise specified in the Protocol.

- Maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are, in general, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; subjects' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; subjects' files; and e-records/records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.
- Sending subjects' data, either as unique samples, copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
  - As required by privacy and data protection regulations and Incyte's privacy policies, if any photographs of subjects are to be used in the study, even if occasionally, or are to be taken, the photographs must be limited to the area of the face or the body that is strictly necessary and the photographs should be masked (ie, identifying features such as eyes, mouth, scars, tattoos, or unique markings or features should be either obscured with a black bar or digitally pixelated so as to not permit the reidentification of the subjects and preserve their confidentiality) by a specially designated photography vendor prior to sending the photographs to Incyte or any other third-party vendors for analysis or further processing.

  - In accordance with French regulations, sites in France must perform the masking before the photographs are transferred, including to any specially designated photography vendor, Incyte, or any other third-party vendors for analysis or further processing. In addition, the subject's specific consent for photographs shall be collected.

- 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.

10.4. Data Quality Assurance

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations). The sponsor or designee is responsible for the data management of this study, including quality checking of the data. Further, monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues, Protocol deviations, and monitoring techniques (eg, central, remote, or on-site monitoring) are provided in the (monitoring plan).

10.5. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable, and the sponsor operates comprehensive data privacy and data security programs that are applicable to this study. Appropriate notice, or notice and consent (as may be required by each applicable jurisdiction), for collection, use, disclosure, and/or transfer (if applicable) of personal information must be obtained in accordance with local

data protection laws. Appropriate data protection terms that comply with applicable laws will be included in relevant study agreements.

To ensure confidentiality of records and protect personal data, subject names will not be supplied to the sponsor or its designee. Only the subject number will be recorded in the eCRF; 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 appropriate technical and organizational measures as required by local data protection laws.

In the event of a data breach involving subject data, the sponsor or its designee will follow the sponsor's incident response procedures. The precise definition of a data breach varies in accordance with applicable law but may generally be understood as a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data. In accordance with its incident response procedures, the sponsor will assess the breach to consider its notification and remediation obligations under applicable law.

10.6. 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 Clinical 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.

10.7. Publication Policy

By signing the study Protocol, the investigator and their 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.

10.8. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

For Japan, when the trial is completed, the investigator should inform the head of the study site of the completion in writing and submit a written summary of the trial's outcome, and then the head of the study site should promptly inform the IRB and sponsor or designee of the completion in writing.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the Protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further study treatment development.

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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 (not applicable in Japan)
  - transdermal (not applicable in Japan)
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1] (not applicable in Japan)
  - 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 investigational medicinal product (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 method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP trial subject 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. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS (CANADA ONLY)

For Subjects Participating in the Study:

Highly Effective Methods

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 or ligation[2]
- Vasectomy/vasectomised partner[2,3]
- Sexual abstinence[4]

Effective Methods

Effective methods may include barrier methods of contraception (eg, male condom, female condom, cervical cap, diaphragm, contraceptive sponge).

[1] Hormonal contraception may be susceptible to interaction with the investigational medicinal product (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 method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP trial subject 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, Health Canada 2013.

APPENDIX C. CYP3A4 INDUCERS AND INHIBITORS

CYP3A Inducers

Inducers	Therapeutic class
Potent CYP3A Inducers	
Rifampin	Antibiotics
Mitotane	Other Antineoplastics
Avasimibe	Other Antilipemics
Rifapentine	Antibiotics
Apalutamide	Antiandrogens
Phenytoin	Anticonvulsants
Carbamazepine	Anticonvulsants
Enzalutamide	Antiandrogens
St John's Wort extract	Herbal medications
Lumacaftor	Cystic fibrosis treatments
Rifabutin	Antibiotics
Phenobarbital	Anticonvulsants
Moderate CYP3A Inducers	
Ritonavir and St. John's wort	None
Semagacestat	Alzheimer's treatments
Efavirenz	NNRTIs
Tipranavir and ritonavir	Protease inhibitors
Dabrafenib	Kinase inhibitors
Lesinurad	Antigout and uricosuric agents
Bosentan	Endothelin receptor antagonists
Genistein	Food products
Thioridazine	Antipsychotics
Nafcillin	Antibiotics
Talviraline	NNRTIs
Lopinavir	Protease inhibitors
Modafinil	Psychostimulants
Pf-06282999	Myeloperoxidase inactivators
Etravirine	NNRTIs
Lersivirine	NNRTIs
Telotristat ethyl	Antidiarrheals

CYP3A Inhibitors

Inhibitor	Therapeutic Class
Potent CYP3A Inhibitors	
VIEKIRA PAK	Antivirals
Indinavir/RIT	Protease inhibitors
Tipranavir/RIT	Protease inhibitors
Ritonavir	Protease inhibitors
Cobicistat (GS-9350)	None
Ketoconazole	Antifungals
Indinavir	Protease inhibitors
Troleandomycin	Antibiotics
Telaprevir	Antivirals
Danoprevir/RIT	Antivirals
Elvitegravir/RIT	Treatments of AIDS
Saquinavir/RIT	Protease inhibitors
Lopinavir/RIT	Protease inhibitors
Itraconazole	Antifungals
Voriconazole	Antifungals
Mibefradil	Calcium channel blockers
LCL161	Cancer treatments
Clarithromycin	Antibiotics
Posaconazole	Antifungals
Telithromycin	Antibiotics
Grapefruit juice DS	Food products
Conivaptan	Diuretics
Nefazodone	Antidepressants
Nelfinavir	Protease inhibitors
Saquinavir	Protease inhibitors
Ribociclib	Kinase inhibitors
Idelalisib	Kinase inhibitors
Boceprevir	Antivirals

Inhibitor	Therapeutic Class
Moderate CYP3A Inhibitors	
Erythromycin	Antibiotics
Fluconazole	Antifungals
Atazanavir/RIT	Protease inhibitors
Darunavir	Protease inhibitors
Diltiazem	Calcium channel blockers
Darunavir/RIT	Protease inhibitors
Dronedarone	Antiarrhythmics
Crizotinib	Kinase inhibitors
Atazanavir	Protease inhibitors
Letermovir	Antivirals
GSK2647544	Alzheimer's disease & dementia treatments
Aprepitant	Antiemetics
Casopitant	Antiemetics
Amprenavir	Protease inhibitors
Faldaprevir	Antivirals
Imatinib	Antineoplastic agents
Verapamil	Calcium channel blockers
Netupitant	Antiemetics
Nilotinib	Kinase inhibitors
Grapefruit juice	Food products
Tofisopam	Benzodiazepines
Cyclosporine	Immunosuppressants
ACT-178882	Renin inhibitors
Ciprofloxacin	Antibiotics
Magnolia vine (Schisandra sphenanthera)	Herbal medications
Isavuconazole	Antifungals
Cimetidine	H-2 receptor antagonists
FK1706	Central nervous system agents

In Vivo CYP3A Inducers

Inducers	Therapeutic class	Object (oral, unless otherwise specified)	% ↓ AUC	% ↑ oral CL	Precipitant Dose (oral)
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)
mitotane	Other Antineoplastics	midazolam	94.5	Not Provided	maximum of 3.5 g TID (chronic therapy)
avasimibe	Other Antilipemics	midazolam	93.5	Not Provided	750 mg/day (7 days)
phenytoin	Anticonvulsants	nisoldipine	89.5	Not Provided	200-450 mg/day (chronic treatment)
carbamazepine	Anticonvulsants	quetiapine	86.6	643.1	200 mg TID (26 days)
enzalutamide	Antiandrogens	midazolam	85.9	Not Provided	160 mg QD (85±3 days)
St John's Wort	Herbal Medications	midazolam	80.0	Not Provided	300 mg TID (14 days)
rifabutin	Antibiotics	delavirdine	Not Provided	458.0	300 mg QD (14 days)
phenobarbital	Anticonvulsants	verapamil	76.6	400.9	100 mg QD (21 days)

APPENDIX D. PHARMACOKINETIC ANALYTICAL PARAMETERS

C_{ave}	Average steady-state plasma concentration ($AUC_{0\text{-}12h}$/12h or $AUC_{0\text{-}24h}$/24h)
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration during the dosing interval
T_{max}	Time to maximum plasma concentration
$AUC_{0\text{-}t}$	Area under the single-dose plasma concentration-time curve from Hour 0 to the last quantifiable measurable plasma concentration, calculated by the linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations
$AUC_{0\text{-}\tau}$ (ie, $AUC_{0\text{-}12h}$ or $AUC_{0\text{-}24h}$)	Area under the steady-state plasma concentration-time curve over 1 dosing interval (ie, from Hour 0 to 12 for BID administration or from Hour 0 to 24 for QD administration), calculated by the linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations
λ_z	Apparent terminal phase disposition rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
$t_{½}$	Apparent plasma terminal phase disposition half-life (whenever possible), where $t_{½} = (\ln 2) / \lambda_z$
Cl/F	Oral dose clearance
V_z/F	Apparent oral dose volume of distribution
Fluctuation	Steady-state fluctuation ($[C_{max} – C_{min}]/C_{ave}$)

In addition, the following PK parameters may be calculated, whenever possible, for each subject based on the urine pemigatinib concentrations:

A_e	Amount of drug excreted in the urine over sampling interval
Cl_r	Renal clearance, where $Cl_r = A_e/AUC$
% Excreted or f_e	percent excreted in the urine, where % Excreted = 100 (A_e/dose)

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as WinNonlin®. Additional details of analyses will be described in the Statistical Analysis Plan.

APPENDIX E. RESPONSE CRITERIA FOR MYELOID/LYMPHOID NEOPLASMS WITH FGFR1 REARRANGEMENT

Table E1: Response Criteria

Response Subcategory	Response Criteria
CR[a]	Presence of all of the following improvements: 1. Bone marrow: ≤ 5% myeloblasts (including monocytic blast equivalent) and no lymphoblasts, with normal maturation of all cell lines, and return to normal cellularity[b]. 2. Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (Grade 1 or less fibrosis)[c] 3. Peripheral blood[d] – WBC ≤ 10×10^9 cells/L. – Hgb ≥ 11 g/dL. – Platelets ≥ 100×10^9/L; ≤ 450×10^9/L. – Neutrophils ≥ 1.0×10^9/L. – Blasts = 0%. – Neutrophil precursors reduced to ≤ 2%. – Monocytes ≤ 1×10^9/L. – Eosinophils ≤ 0.5×10^9/L. 4. Extramedullary disease: Complete resolution of extramedullary disease present before therapy (eg, lymphadenopathy), including palpable hepatosplenomegaly. NOTE: Persistent low-level dysplasia is permitted given subjectivity of assignment of dysplasia[b].
PR	Presence of all of the following improvements: 1. Reduction of bone marrow blasts (and blast equivalents) by 50%, but remaining > 5% of cellularity (except in cases with ≤ 5% bone marrow blasts at baseline). 2. Normalization of peripheral blood indices listed in CR Criterion 3. 3. Extra medullary disease response of CMR/CR or PMR/PR (see Table E2).
Progression of disease	Combination of 2 major criteria, 1 major and 2 minor criteria, or 3 minor criteria from following lists: **Major criteria:** • Increase in blast counta o < 5% blasts: ≥ 50% increase and to > 5% blasts. o 5%-10% blasts: ≥ 50% increase and to > 10% blasts. o 10%-20% blasts: ≥ 50% increase and to > 20% blasts. o 20%-30% blasts: ≥50% increase and to > 30% blasts. • Evidence of cytogenetic evolution o Re-appearance of a previously present or appearance of a new cytogenetic abnormality in complete cytogenetic remission via classic karyotyping or FISH. o Increase in cytogenetic burden of disease in partial cytogenetic remission by ≥ 50% via classic karyotyping or by ≥ 50% and involving at least 10% (eg, 2/200) of cells via FISH.

Table E1: Response Criteria (Continued)

Response Subcategory	Response Criteria
Progression of disease (continued)	• New or worsening extramedullary disease o Worsening splenomegaly ▪ Progressive splenomegaly that is defined by IWG-MRT: the appearance of a previously absent splenomegaly that is palpable at > 5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5 to 10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of > 10 cm. o Extramedullary disease outside of the spleen. **Minor criteria:** • Transfusion dependence.[e] • Significant loss of maximal response on cytopenias ≥ 50% decrement from maximum remission/response in granulocytes or platelets. • Reduction in Hgb by ≥ 1.5g/dL from best response or from baseline as noted on complete blood count. • Evidence of clonal evolution (molecular).
Stable disease	Meeting neither progression of disease nor response criteria. Subjects with stable disease will be further characterized according to criteria presented in Table E3.
Cytogenetic Response[f]	
Complete (cCyR)	0% 8p11 translocated metaphases as seen on classic karyotyping with minimal of 20 metaphases, or FISH.
Partial (pCyR)	Decrease from baseline of 50% or more 8p11 translocated metaphases as seen on classic karyotyping with minimal of 20 metaphases, or FISH.

CR = complete response; FISH = fluorescence in situ hybridization; Hgb = hemoglobin; IWG-MRT = International Working Group-Myeloproliferative Neoplasms Research and Treatment; PR = partial response; WBC = white blood cell.

[a] Given the current lack of a validated tool to assess complete resolution of symptoms, "CR with resolution of symptoms" (a complete resolution of disease-related symptoms as noted by the MPN-SAF in presence of CR) will be a provisional category of disease response.

[b] Presence of dysplastic changes, which may be interpreted within the scope of normal range of dysplastic changes, may still exist in the presence of CR as allowed in MDS IWG. Marrow should exhibit age-adjusted normocellularity in CR.

[c] The assessment of CR must be confirmed by a minimum of 2 bone marrow assessments only to confirm improvement in fibrosis. If there is no significant fibrosis present on the initial bone marrow biopsy, then a second biopsy is not required to prove resolution of fibrosis. Grading of fibrosis in measurement of treatment response should be according to the European Consensus System.

[d] Resolution of abnormal peripheral blood counts must persist for at least 2 separate analyses over at least 8 weeks. In the case of proliferative disease, CR will include resolution of thrombocytosis to a normal platelet count (150-450 × 10^9/L) and resolution of leukocytosis to WBC ≤ 10 × 10^9 cells/L but ≥ 1.5 × 10^9/L. Hemoglobin should be maintained > 11 g/dL and platelets ≥ 100 × 10^9/L without the support of transfusions. Reduction in myeloid precursors (promyelocytes, myelocytes, metamyelocytes, nucleated red blood cells) to less than appreciable levels (≤ 2%-3%) and/or 1 × 10^9/L monocytosis and/or eosinophils ≤ 0.5 × 10^9/L in the absence of infection, cytokine treatment, or other reactive causes.

[e] Transfusion dependency is defined by a history of at least 2 U of red blood cell transfusions in the past month for a hemoglobin level < 8.5 g/dL that was not associated with clinically overt bleeding. Cytopenias resulting from therapy should not be considered in assessment of progression.

[f] Loss of cytogenetic burden of disease by (via FISH or classic karyotyping) is required to reach complete cytogenetic response. Decrease in the cytogenetic burden of disease must be by ≥ 50% (via FISH or classic karyotyping) to be indicative of a partial cytogenetic response. Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on the performance characteristics of the specific probes used.

Table E2: Extramedullary Disease Response Criteria

Assessment	PET-CT Based	CT Based
CMR/CR		
Target	A 5PS score of 1, 2, or 3, w/ or w/o residual mass. Additionally, if screening FDG-PET scan is missing & on-study 5PS score is 1-3, then CMR is possible.	Nodal: < 1.5 cm in LDi. Extra-nodal: Absent.
Non-target		Absent.
New lesions	None.	
PMR/PR		
Target	5PS score of 4 or 5 with reduced FDG uptake compared to baseline and residual masses of any size. Note: Reduced uptake defined as ≥ 25% decrease in $\%\Delta SUV_{max}$.	≥ 50% decrease from baseline in SPD of all target lesions.
Non-target		No increase.
New lesions	None.	
NMR/SD		
Target	5PS score of 4 or 5 with no significant change in FDG uptake compared to baseline and residual masses of any size. Note: "No significant change in uptake" defined as the criteria of PMR/PMD not being met.	< 50% decrease from baseline in SPD of all target lesions. No PD criteria met.
Non-target		No progression.
New lesions	None.	
PMD/PD		
Target	5PS score of 4 or 5 with significant increase in FDG uptake, defined as ≥ 50% increase in the $\%\Delta SUV_{max}$ of the most FDG-avid disease.	Node or lesion must be abnormal with an LDi > 15 mm, an increase by ≥ 50% from nadir PPD, and an increase in LDi or SDi from nadir by: • At least 5 mm for lesions measuring ≤ 20 mm or • At least 10 mm for lesions measuring > 20 mm.
Non-target		Unequivocal progression.
New lesions	New or recurrent markedly diffuse FDG-avid uptake in the liver or spleen.	• Regrowth of previously resolved lesions. • New node > 1.5 cm in any axis. • New extranodal site > 1.0 cm in any axis.

5PS = Deauville 5-point scale; CMR = complete metabolic response; CR = complete response; CT = computed tomography; FDG = fludeoxyglucose; LDi = longest transverse diameter of lesion; NMR = no metabolic response; PD = progressive disease; PET = positron emission tomography; PMD = progressive metabolic disease; PMR = partial metabolic response; PPD = product of perpendicular diameters; PR = partial response; SD = stable disease; SDi = shortest axis perpendicular to LDi; SPD = sum of product of perpendicular diameters of multiple lesions; SUV = standardized uptake value.

Table E3: Characteristics of Stable Disease

Characteristic	Criteria
CHR	Peripheral blood normalization as in CR Criterion 3 (Table E1; peripheral blood response must be verified at ≥ 8 weeks)
Marrow response	• Complete marrow response: Presence of all marrow criteria listed in CR criterion without normalization of peripheral blood indices listed in CR Criterion 2. • Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining > 5% of cellularity, or reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations spaced at least 2 months apart.
Clinical benefit	Requires 2 of the following in the absence of progression or CR/PR and independent of marrow response (peripheral blood response must be verified at ≥ 8 weeks) to be considered a clinical benefit: Erythroid response: • Hgb increase by ≥ 2.0 g/dL. • TI for > 8 weeks for patients requiring at least 4 packed red blood cell transfusions in the previous 8 weeks. • Only red blood cell transfusions given based on physician's judgment for a pretreatment Hgb of ≤ 8.5 g/dL will count in the red blood cell TI response evaluation.[a] Platelet response: • Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 weeks. • Pretreatment ≤ 20×10^9/L: Increase from < 20×10^9/L to > 20×10^9/L and by at least 100%. • Pretreatment > 20×10^9/L but ≤ 100×10^9/L: absolute increase of ≥ 30×10^9/L.[a] Neutrophil response: • Pretreatment ≤ 0.5×10^9/L: At least 100% increase and an absolute increase ≥ 0.5×10^9/L. • Pretreatment > 0.5×10^9/L and ≤ 1.0×10^9/L: At least 50% increase and an absolute increase ≥ 0.5×10^9/L.[a] Eosinophil response: • Normalization if pretreatment > 0.5×10^9/L.[a] Extramedullary disease response: • As defined in Table E2.
Symptom response	Improvement in symptoms as noted by decrease of ≥ 50% as per the MPN-SAF scoring; subjects scoring < 20 at baseline were not considered eligible for measuring clinical benefit.

CR = complete response; CHR = complete hematologic response; Hgb = hemoglobin; PR = partial response; TI = transfusion independence.

[a] Resolution of abnormal peripheral blood counts must persist for at least 2 separate analyses over at least 8 weeks. In the case of proliferative disease, CR will include resolution of thrombocytosis to a normal platelet count (150-450 × 10^9/L) and resolution of leukocytosis to WBC ≤ 10×10^9 cells/L but ≥ 1.5×10^9/L. Hemoglobin should be maintained > 11 g/dL and platelets ≥100×10^9/L without the support of transfusions. Clinical benefit may occur when these changes occur in absence of other changes required for CR or marrow response. Platelet and packed red blood cell TI would be considered for clinical benefit, and duration of TI should be monitored. Reduction in myeloid precursors (promyelocytes, myelocytes, metamyelocytes, nucleated red blood cells) to less than appreciable levels (≤ 2%-3%) and/or 1×10^9/L monocytosis in the absence of infection, cytokine treatment, or other reactive causes.

APPENDIX F. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

The COVID-19 global pandemic presents numerous challenges to the ongoing conduct of clinical trials. In line with the European Medicines Agency's Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic (2020), the sponsor has issued the following Protocol considerations to ensure subject safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain.

Recognizing the flexibility required to manage the impact of the pandemic on this clinical trial, additional details will be added to respective study manuals, project plan documents, and communicated to the investigative sites as needed.

Study Site Visits

If local travel restrictions, isolation requirements, or the investigator's benefit/risk assessment determines it to be unsafe for subjects to attend study visits at the investigational site, the site staff may elect to pursue the following:

- In order to minimize subject risk, study visits may be conducted via telemedicine modalities (phone or video). At a minimum, a review of AEs, concomitant medications, and study drug compliance must be completed. Periodic on-site visits should be conducted whenever feasible.
- In order to support investigator oversight of subject safety and disease management, the subject may be asked to perform some laboratory tests or study procedures (eg, eye exam) in a local (proximate) hospital laboratory or facility closer to the subject's residence rather than at the investigational site. In this case, the study physician will provide the subject with the list of parameters to be checked. These tests should be carried out in certified laboratories.

Investigational Medicinal Product Dispensation and Distribution

In order to ensure the continuity of providing their subjects' clinical supplies within the constraints imparted by the pandemic, the site staff can decide to supply IMP to subjects as follows:

- Where possible, when the subject attends a visit at the study site, the investigator can dispense an additional amount of pemigatinib tablets to cover a longer interval between on-site study visits than stipulated in the schedule of assessments (see Table 4).
- Alternatively, if the subject cannot attend a visit at the study site, adequate supplies of IMP to cover 1 or more cycles can be shipped to the subject by the investigator or appropriately delegated staff (eg, the study pharmacy staff) using a third party service if duly authorized by the subject. The study site may use their own preferred courier, provided the courier adheres to certain standards (eg, use of personal protection equipment, maintenance of temperature-controlled transit environment), or one centrally contracted by the sponsor.

Clinical Trial Monitoring

Study monitoring visits could be postponed; however, the site monitor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, emails, video visits) with the sites to get information on trial progress, subject status, and information on issue resolution. The study monitor may remotely review data entered into the EDC for accuracy and completeness. Remote source data verification may be implemented with agreement of the principal investigator and institution, as applicable.

If the study site monitor cannot be on-site to carry out the final drug accountability for reconciliation purposes, and the operation cannot be postponed, it may be carried out by a pharmacist from the hospital pharmacy or by the study coordinator/data manager with suitable training. The IMP can be returned to the sponsor by the hospital pharmacy directly, or destroyed in accordance with local practices, if applicable, and with sponsor approval.

Direct Contracts With Third Parties/Specialized Service Companies

If necessary, direct contracts can be established with third-party local physicians to conduct activities related to the clinical management of subjects for whom the investigator is responsible and maintains oversight. In such situations, the investigator is required to provide the local physician with a delegation letter listing all delegated activities. The sponsor, through the study investigator or institution, will reimburse the local physician for the test/procedures conducted outside of the standard of care.

Reimbursement of Extraordinary Expenses

The sponsor will arrange to reimburse subjects for any extraordinary expenses, keeping appropriate documentation as evidence (eg, travel expenses for the local laboratory visit(s), the costs of local [proximate] laboratory tests).

APPENDIX G. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1	09 AUG 2016
Amendment (Version) 2	12 DEC 2016
Amendment (Version) 3	17 MAY 2018
Amendment (Version) 4	22 MAY 2019
Amendment (Version) 5	02 JUL 2020
Amendment (Version) 6	13 JUL 2023

Amendment 6 (13 JUL 2023)

Overall Rationale for the Amendment:

The main purpose of this amendment is to modify the long-term treatment visit schedule to start at Cycle 18 and to update the assessments in post-transplant follow-up period. This amendment also incorporates changes from local adaptations for Germany (Amendment 4-DE), Canada (Amendment 4-CA), and Japan (Amendment 4-JP). Changes from Amendment 5-DE, Amendment 5-CA, and Amendment 5-JP are consistent with the changes in Protocol Amendment 5 (dated 02 JUL 2020). Additional changes are summarized below.

1. **Synopsis**

   Description of change: Updated principal coordinating investigator.

   Rationale for change: Coordinating investigator changed from Srdan Verstovsek, MD to Jason Gotlib, MD.

2. **Synopsis; Section 2.2.3, Exploratory Endpoints; Section 6, Study Assessments (Table 4: Study Assessments); Section 7.7.2, Quality-of-Life Assessment**

   Description of change: Clarified that quality-of-life assessments will be collected until each subject is on study for at least 12 months.

   Rationale for change: To update the length of collection of quality-of-life assessments.

3. **Synopsis; Section 6, Study Assessments (Table 4: Study Assessments; Table 5: Laboratory Assessments); Section 6.4.2.1, Post-Transplant Follow-Up; Section 7.6.2, Bone Marrow Exams and Cytogenetics (Table 7: Bone Marrow Exam Schedule)**

   Description of change: Clarified that subjects who bridge to transplant should also have bone marrow biopsy and aspirate and peripheral blood smears, CBCs, and differentials at 1 to 3 months and 6 months post-transplant and then as per local standard of care.

   Rationale for change: To allow for the assessment of responses post-transplant.

4. **Synopsis; Section 6, Study Assessments (Table 5: Laboratory Assessments); Section 7.5.6, Laboratory Assessments**

   Description of change: Changed to indicate lipid panel will only be analyzed at Cycle 1 Day 1.

   Rationale for change: No safety issues identified across studies with pemigatinib and to be consistent with the other pemigatinib Protocols.

5. **Synopsis; Section 6.2.1, Long-Term Treatment Visit Schedule**

   Description of change: Modified the long-term treatment visit schedule to start at Cycle 18 for subjects who meet the Protocol-defined criteria.

   Rationale for change: To ease subject burden.

6. **Section 1.1.1, Fibroblast Growth Factor Receptor Inhibition in Oncology; Section 1.2, Study Rationale; Section 1.3.2, Potential Risks of Pemigatinib Based on Clinical Safety**

   Description of change: Updated based on recently published data.

   Rationale for change: To update with more relevant publications regarding FGFR inhibition in oncology and incorporate data based on the most recent IB.

7. **Section 3.1, Subject Inclusion Criteria (Criterion 1)**

   Description of change: Language regarding the age of subjects in Japan, which was originally added in Protocol Amendment 4-JP, has been removed.

   Rationale for change: Effective 01 APR 2022, the age of adulthood in Japan changed from ≥ 20 years to ≥ 18 years.

8. **Section 3.1, Subject Inclusion Criteria (Criteria 6b and 6c); Appendix B, Information Regarding Effectiveness of Contraceptive Measures (Canada Only)**

   Description of change: Modified language and added Appendix B to require the use of a highly effective method of contraception in combination with an effective method (barrier method) of preventing pregnancy.

   Rationale for change: To conform to Canadian Health Authority contraceptive guidance in clinical trials of teratogenic products.

9. **Section 4.5, Overall Study Duration**

   Description of change: Language was added to indicate the potential end of study, which should occur when the last subject enrolled has been followed for 24 months.

   Rationale for change: To define the duration of follow-up and potential end of study.

10. **Section 4.6, Study Termination**

    Description of change: Added language specific to Japan.

    Rationale for change: PMDA requirement.

11. **Section 5.4.3, Management of Hyperphosphatemia**

    Description of change: Added the recommended phosphate binder for Japan and indicated it is provided by the sponsor.

    Rationale for change: To continue providing lanthanum carbonate hydrate after commercially available for hyperphosphatemia associated with FGFR inhibitor–treatment.

12. **Section 6, Study Assessments (Table 4: Study Assessments)**

    Description of change: Tissue sources for the optional EMD biopsy were expanded to include extranodal locations.

    Rationale for change: The disease under study may manifest in extramedullary locations beyond the lymph nodes, this update allows for extranodal sites of EMD to be considered for tissue biopsy collection.

13. **Section 6, Study Assessments (Table 4: Study Assessments); Section 7.5.4, Electrocardiograms**

    Description of change: Frequency of ECGs was reduced to every 3 cycles or more often if clinically indicated.

    Rationale for change: Based on data from Study INCB 54828-101 (Gong et al 2022), pemigatinib does not exhibit any clinically significant prolongation of QTc or dose-dependent changes in heart rate. Consistent with other pemigatinib Protocols, the frequency of ECGs was reduced.

14. **Section 6, Study Assessments (Table 5: Laboratory Assessments)**

    Description of change: Clarified that sample collection for correlative assessments will be decreased to the same schedule as bone marrow samples and efficacy assessments.

    Rationale for change: To ease subject burden.

15. **Section 8.3.1, Definitions**

    Description of change: The SAE definition criteria were updated to include events that may lead to disability.

    Rationale for change: PMDA requirement.

16. **Section 8.3.2, Reporting**

    Description of change: Added language to clarify requirements for the reporting of SAEs to the head of the site and Japanese regulatory reporting.

    Rationale for change: PMDA requirement.

17. **Section 8.8, Product Complaints**

    Description of change: Added language to require the site to report medical device–related complaints.

    Rationale for change: PMDA requirement.

18. **Section 10.1, Investigator Responsibilities**

    Description of change: Added language to stipulate the record retention period per J-GCP guidelines.

    Rationale for change: J-GCP requirement.

19. **Section 10.2, Accountability, Handling, and Disposal of Study Drug**

    Description of change: Added the investigational drug storage manager per J-GCP guidelines.

    Rationale for change: J-GCP requirement.

20. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

    Description of change: Added language to clarify unapproved contraceptive methods in Japan.

    Rationale for change: To clarify the appropriate methods approved in Japan.

21. **Appendix F, COVID-19 Pandemic Mitigation Strategies and Instructions**

    Description of change: Appendix F was added.

    Rationale for change: To provide sites with guidance in response to the COVID-19 pandemic.

22. **Incorporation of administrative changes.** Other regulatory guidance and administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 5 (02 JUL 2020)

Overall Rationale for the Amendment:

The main purpose of this amendment is to include updated language for comprehensive eye examination, per FDA feedback. Other modifications have been made to include a long-term treatment visit schedule option for subjects with stable response, to update the Protocol with program-level standard language and post-transplant follow-up, and to provide additional language clarifications.

1. **Synopsis; Section 6, Study Assessments (Table 4: Study Assessments; Table 5: Laboratory Assessments); Section 6.2.1, Long-Term Treatment Visit Schedule; Section 7.5.6.1, Pregnancy Testing**

   Description of change: Language was added to provide subjects who have been on study treatment for more than 78 weeks (18 months), have had a stable clinical and cytogenetic response and manageable adverse events the option to extend study visit frequency to every 3 cycles (9 weeks).

   Rationale for change: To ease subject's long-term study visit burden.

2. **Section 5.4.2, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug; Section 5.4.3, Management of Hyperphosphatemia; Section 5.4.5, Criteria for Permanent Discontinuation of Study Drug**

   Description of change: Added pemigatinib program standard language.

   Rationale for change: To conform to pemigatinib development standard language.

3. **Section 6, Study Assessments (Table 6: Required Analytes); Section 7.5.6.2, Hepatitis Screening Tests**

   Description of change: Clarified hepatitis screening requirements.

   Rationale for change: To clarify Protocol.

4. **Section 6, Study Assessments (Table 4: Study Assessments); Section 6.4.2.1, Post-Transplant Follow-Up; Section 7.6.2, Bone Marrow Exams and Cytogenetics (Table 7: Bone Marrow Exam Schedule)**

   Description of change: Added language regarding standard of care data to be collected following subjects who successfully bridge to transplant. Added language relative to post-transplant efficacy assessments, including bone marrow examinations.

   Rationale for change: Post-transplant status data added per FDA request. Post-transplant bone marrow examinations added at the end of the post-transplant follow-up period to allow for a final comprehensive efficacy analysis.

5. **Section 6, Study Assessments (Table 4: Study Assessments); Section 7.5.5, Comprehensive Eye Examination**

   Description of change: Language added to indicate that OCT is mandatory at baseline and every 3 cycles and EOT as part of the eye examination process.

   Rationale for change: Required program-wide per FDA feedback.

6. **Synopsis; Section 6, Study Assessments (Table 4: Study Assessments; Table 5: Laboratory Assessments); Section 7.6, Efficacy Assessments**

   Description of change: Section edited to provide greater detail regarding efficacy assessments.

   Rationale for change: To clarify section for investigators.

7. **Appendix D, Response Criteria for Myeloid/Lymphoid Neoplasms With FGFR1 Rearrangement**

   Description of change: Deleted osteomyelosis grading as a criterion for partial response.

   Rationale for change: The criterion is not needed in the definition of a partial response.

8. **Incorporation of administrative changes.** Other minor, administrative changes and clarifications have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 4 (22 MAY 2019)

Overall Rationale for the Amendment:

The main purpose of this amendment is to modify the primary and secondary study efficacy endpoints and to revise the proposed response criteria. Other modifications have been made to include treatment-naive subjects and to update the Protocol with program-level standard language.

1. **Synopsis; Section 1.1.2, Myeloid/Lymphoid Neoplasms With FGFR1 Rearrangement; Section 2, Study Objectives and Endpoints; Section 9.2, Selection of Sample Size; Section 9.4.1, Efficacy Analyses**

   Description of change: The primary efficacy endpoint was modified to include only the proportion of subjects who achieve a complete response. Secondary endpoints measuring the rates of response and cytogenetic response were added, as were secondary endpoints of duration of complete response and duration of response. An exploratory efficacy endpoint to describe potential indicators of clinical benefit in subjects [redacted]

   Rationale for change: To evaluate the efficacy of study treatment according to a more conventional endpoint.

2. **Appendix D, Response Criteria for Myeloid/Lymphoid Neoplasms With FGFR1 Rearrangement**

   Description of change: The response criteria table was revised to clarify the groupings of the response categories. Additionally, criterion to evaluate residual fibrosis in the bone marrow was added to the complete and partial response criteria, and the extramedullary disease response criterion was modified in the definition of partial response. Table D2 was added to provide guidance on evaluating extramedullary disease response, and Table D3 was added to list the characterizing criteria of stable disease.

   Rationale for change: Criteria have been revised based on investigator and external expert feedback.

3. **Synopsis; Section 3.1, Subject Inclusion Criteria**

   Description of change: Inclusion Criterion 3 was revised to include treatment-naive subjects who are not current candidates for stem cell transplants or other disease-modifying therapies.

   Rationale for change: There is no current standard-of-care therapy to treat the disease under study, and with the clinical activity observed to date, it is worth evaluating treatment with pemigatinib in treatment-naive subjects.

4. **Synopsis; Section 1.3.2.1, Pharmacokinetic/Pharmacodynamic Summary; Section 4.1, Overall Study Design; Section 5.4.4, Up-Titration; Section 6, Study Assessments (Table 4: Study Assessments; Table 5: Laboratory Assessments)**

   Description of change: Language describing the rationale, criteria, and process for dose up-titration was added.

   Rationale for change: To allow up-titration for subjects without hyperphosphatemia due to correlation with low drug exposure.

5. **Synopsis; Section 1.3.2, Potential Risks of Pemigatinib Based on Clinical Safety; Section 1.3.2.1, Pharmacokinetic/Pharmacodynamic Summary; Section 5.2.1.1, Description and Administration; Section 5.2.1.4, Instruction to Subjects for Handling Study Drug; Section 5.6.1, Restricted Medications; Section 5.6.2, Prohibited Medications; Section 8.1.1, Definitions; Section 8.1.2 Reporting; Section 8.3.1 Definitions; Appendix B, CYP3A4 Inducers and Inhibitors**

   Description of change: Study drug administration and handling instructions were updated based on preliminary food-effect study data. Clinical safety, pharmacokinetic and pharmacodynamics data were updated according to the current IB. Language regarding restricted and prohibited medications was updated to align with current program standards. Adverse event definition language was updated according to current company standards.

   Rationale for change: To align protocol language with current compound, program, and company standards.

6. **Synopsis; Section 6, Study Assessments (Table 4: Study Assessments; Table 6: Laboratory Assessments: Required Analytes); Section 6.4.2, Disease Status Follow-Up; Section 7.6, Efficacy Assessments; Section 7.6.1, Assessment of Disease Response**

   Description of change: The frequency of disease assessments in the disease status follow-up study period was clarified. Allowance for an automated hematology differential was added. The schedule of bone marrow exams and PET-CT scans was changed to reference weeks on study. The criteria to repeat cytogenetic exams was modified. Clarification regarding recording of flow cytometry data was added. Protocol language relevant to disease imaging studies was clarified. Language regarding the assessment of disease response by investigators and by central review was added.

   Rationale for change: To clarify language concerning disease assessments and to introduce language regarding the central review committee.

7. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 3 (17 MAY 2018)

Overall Rationale for the Amendment:

The purpose of this amendment is to add language to allow for continuous administration of INCB054828. Updated clinical data have been added to support continuous administration. Other modifications have been made based on new preclinical and/or clinical data.

1. **Synopsis; Section 1.2, Study Rationale, Section 4.1, Overall Study Design; Section 5.2.1.1, Description and Administration**

   Description of change: Language has been added to allow for continuous administration of INCB054828.

   Rationale for change: Addition of 13.5 mg continuous administration regimen into the study.

2. Synopsis; Section 3.2, Subject Exclusion Criteria

   Description of change: Exclusion criteria 3, 14, and 15 have been updated/language refined.

   Rationale for change: These criteria have been updated based on new guidelines (criterion 3) and more clinical and preclinical experience with INCB054828 (criteria 14 and 15).

3. **Section 1.3.2, Potential Risks of INCB054828 Based on Clinical Safety**

   Description of change: Updated exposure and safety data from study INCB 54828-101 have been added.

   Rationale for change: To provide more safety data for continuous administration of INCB054828.

4. **Section 1.3.2.1, Pharmacokinetics and Pharmacodynamics Summary**

   Description of change: Language has been added regarding PK profile of INCB054828 continuous administration compared to intermittent administration.

   Rationale for change: To provide PK data to support continuous administration of INCB054828.

5. **Section 1.3.3, Phototoxicity**

   Description of change: The section has been changed to indicate no precautions are needed.

   Rationale for change: Results of toxicology studies support that no precautions are necessary.

6. **Section 5.6.1, Restricted Medications**

   Description of change: Deleted p-glycoprotein substrates.

   Rationale for change: Based on updated preclinical and early clinical data, p-glycoprotein substrates are no longer restricted.

7. **Section 7.5.5, Comprehensive Eye Examination**

   Description of change: Language has been added to include additional testing that is both required at all visit and if clinically indicated.

   Rationale for change: Additional baseline assessments are required and optical coherence tomography is required if clinical ocular symptoms are present during examination.

8. **Section 6, Study Assessments (Table 5, Laboratory Assessments); Section 7.9.5, Buccal Swab**

   Description of change: Buccal swab assessment has been deleted.

   Rationale for change: Samples from buccal swabs are no longer required.

9. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 2 (12 DEC 2016)

The primary purpose of this amendment is to update language based on Regulatory Agencies comments. Updates include but are not limited to clarification of inclusion and exclusion criteria and guidance for dose reductions.

1. **Synopsis; Section 3.1, Subject Inclusion Criteria**

   Description of change: Language was added to inclusion criterion 3 (defining the eligible population) to provide clearer explanation of subjects allowed to be enrolled.

   Rationale for change: Updated per Regulatory Agency request.

2. **Synopsis; Section 6, Study Assessments (Table 6, Laboratory Assessments; Table 7, Laboratory Assessments: Required Analytes); Section 7.5.6.1, Pregnancy Testing**

   Description of change: Added urine pregnancy test on Day 1 of every cycle before dose administration.

   Rationale for change: Updated to test for pregnancy before the start of each cycle.

3. **Section 1.3.3, Phototoxicity**

   Description of change: This section was added to include language regarding potential phototoxicity of INCB054828.

   Rationale for change: Cautionary update based on the unknown phototoxicity risk associated with INCB054828.

4. **Section 3.1, Subject Inclusion Criteria; Section 3.2, Subject Exclusion Criteria**

   Description of change: Inclusion criterion #6c and exclusion criterion #12 have been revised to include text to ensure that male subjects continue using contraception for 90 days after last dose (1 sperm cycle).

   Rationale: Updated per Regulatory Agency request.

5. **Section 3.2, Subject Exclusion Criteria**

   Description of change: The original exclusion criterion 4 was deleted. Subjects who had bone marrow transplantation within the past 12 months will no longer be excluded, and the exclusion for chronic graft-versus-host disease requiring systemic treatment is now covered under the revised inclusion criterion 3.

   Rationale for change: The Protocol will allow subjects who have recurred after transplant.

6. **Section 5.4.2, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug; Section 5.4.3, Management of Hyperphosphatemia**

   Description of change: Added language to provide more instructions for dose reductions.

   Rationale for change: Updated per Regulatory Agency request.

7. **Section 6, Study Assessments (Table 5, Schedule of Assessments)**

   Description of change: Note was added for post-treatment bone marrow biopsy/aspirate to clarify that it is only required at disease status follow-up (every 9 weeks) for subjects who do not discontinue due to progressive disease. It is not required at survival follow-up.

   Rationale for change: The previous version of the protocol incorrectly indicated bone marrow biopsy/aspirate for survival follow-up (every 12 weeks) in addition to disease status follow-up (every 9 weeks) and did not provide enough clarity on subjects for whom it is required.

8. **Section 6, Study Assessments (Table 5, Schedule of Assessments); Section 7.6, Efficacy Assessments**

   Description of change: In Table 5 "Additional Assessments" was changed to PET/CT scan with notes added to qualify the timing and frequency of assessments. The same language was added to Section 7.6.

   Rationale for change: The previous version of the Protocol did not provide enough clarity on expectations for follow-up scans.

9. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the protocol and are noted in the attached red-line/strike-out version of the amendment.

Amendment 1 (09 AUG 2016)

The primary purpose of this Protocol Amendment is to provide additional clinical data from the ongoing INCB 53828-101 study, refine the inclusion criteria to better define the population, and to amend the pharmacokinetic (PK) and electrocardiogram (ECG) sampling timepoint requirements.

1. **Synopsis; Section 3.1, Subject Inclusion Criteria**

   Description of change: Inclusion criterion #2 has been revised to clarify the timing and location of sequencing subjects ("Documented lymphoid or myeloid neoplasm with 8p11 rearrangement known to lead to FGFR1 activation, *based on standard diagnostic cytogenetic evaluation performed locally,* before signing informed consent for this study.") A new inclusion criterion (#3) has been added to define the population to be studied ("*Only subjects who are not candidates for stem cell transplantation and who have progressed and are not candidates for other disease-modifying therapies are eligible for the study.*").

   Rationale for change: Clearer definition of study population and sequencing was added per FDA request.

2. **Section 1.3.2, Potential Risks of INCB054828 Based on Clinical Safety**

   Description of change: Additional data from ongoing study INCB 54828-101 have been added. Exposure data and safety data have been updated.

   Rationale for change: The FDA questioned the starting dose and safety of the starting dose in this study. The additional data provide background for the starting dose and a summary of safety and exposure data to date.

3. **Section 5.6.1, Restricted Medications**

   Description of change: P-glycoprotein substrates were added as restricted medications in this study.

   Rationale for change: Added per FDA request.

4. **Section 6, Study Assessments (Table 5: Study Assessments); Section 7.5.4, Electrocardiograms**

   Description of change: Triplicate ECGs have been added on Cycle 1 Day 1 and Cycle 1 Day 8, paired with PK samples at predose, 1 hour postdose, and 2 hours postdose.

   Rationale for change: Added per FDA request.

5. **Section 6, Study Assessments (Table 6: Laboratory Assessments); Section 7.8.1, Pharmacokinetics**

   Description of change: Pharmacokinetic sampling times have been revised to include sampling on Cycle 1 Day 1. The postdose sample noted in the original Protocol as between hours 1 and 2 will now be 2 samples: 1 sample at 1 hour postdose and 1 sample at 2 hours postdose. The same PK sampling schedule is applied to both Day 1 and Day 8.

   Rationale for change: Revised per FDA request for PK assessment after a single dose (Day 1) and multiple doses (Day 8).

Signature Page for VV-CLIN-000562 v8.0

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Approval Task	[redacted] over [redacted] Oncology Targeted Therapeutics 14-Jul-2023 12:06:35 GMT+0000

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