Study Title:	A Phase 2 open-label study of the CSF-1R inhibitor JNJ-40346527 in patients with relapsed/refractory acute myeloid leukemia (AML)
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SUMMARY OF CHANGES

#	Section	Page(s)	Change	Justification
1	Cover	1	Removed Subsite PIs	Sub-sites are not active at the time of this update
2	Cover	1	Updated Statistician	New Statistician assigned
3	5.1.8.2; 7.1.6	41; 50	Removed references to Appendix D	Removed Appendix D
4	7.2.5;7.2.7	51	Edited Collection Requirements	Clarified SOC collection vs collection for lab
5	7.3.1	52	Changed assay window	Correcting for consistency
6	7.3.3	53	Updated appendix reference	To reference correct appendix
7	Appendix D	86	Removed Study Diary from Protocol	Not needed in protocol if uploaded to IRB separately (allows for easier updates to just the drug diary)
8	F	89	Removed Enrollment Packet from Protocol	Not needed in protocol if uploaded to IRB separately (allows for easier updates to just the Enrollment Packet)
9	Appendix E	86	Renamed to appendix D	Removed prior appendix D

SYNOPSIS

Study Title	A Phase 2 open-label study of the CSF-1R inhibitor JNJ-40346527 in patients with relapsed/refractory acute myeloid leukemia (AML)
Protocol #	17583
Study Center:	multicenter [U.S. only]
Clinical Phase:	Phase II - Single Agent
Investigational Components:	1. In vitro Diagnostic Device 2. Investigational Drug
Interventional Study Type:	*Multi-arm*
Précis:	Targeting and depleting tumor-associated macrophages is emerging as an attractive anti-tumor therapeutic approach, and the CSF-1/CSF-1R pathway is a particularly attractive molecular target to selectively inhibit the recruitment, activation, polarization, and survival of immunosuppressive tumor-associated macrophages. Clinical evidence suggests that drugs targeting intrinsic CSF-1R tyrosine kinase activity provide some degree of clinical benefit. This trial will evaluate the preliminary efficacy of the small molecule inhibitor, JNJ-40346527, which will selectively inhibit CSF-1R tyrosine kinase activity in patients with relapsed or refractory acute myeloid leukemia (AML). The underlying hypothesis is that JNJ-40346527 targets a subpopulation of supportive cells, which leads to interruption of paracrine survival signals to AML cells, and subsequent leukemic cell death. In this study, the sensitivity of participants' AML cells to the CSF-1R inhibitor, JNJ-40346527, will be evaluated using a functional *ex vivo* screening platform. Based on the results of this in vitro drug screen, participants will be assigned to either the study drug sensitive (i.e., Assay positive) or insensitive (i.e., Assay negative) arms. Both arms will receive the same treatment of JNJ-40346527 (150mg, PO *b.i.d*) over a continuous 28 day cycle. Participants will continue to receive study agent until disease progression.
Primary Objectives	Evaluate preliminary efficacy of JNJ-40346527 in participants with relapsed/refractory AML. 1. Best objective response rate (≥PR)
Secondary Objectives	Assess safety and survival associated with JNJ-40346527 to treat participants with relapsed/refractory AML. Assess the duration of disease response associated with JNJ-40346527. 1. Overall incidence of treatment-related and non-treatment related toxicity. 2. Duration of response. 3. 12-month event-free survival. 4. 12-month overall survival.

Exploratory Objectives	1. Evaluate the pharmacokinetics of JNJ-40346527 and effective inhibition of CSF-1R in marrow aspirates using plasma inhibitory assays with established CSF-1R-sensitive cell lines. 2. Identify the effect of JNJ-40346527 on leukemia cells and the immune microenvironment. 3. Analyze the frequency of mutations using genomic DNA from leukemia participants to determine if there is a genetic signature that predicts response to JNJ-40346527. 4. Using RNA sequencing (RNAseq), identify an expression signature in CSF-1R^{+} cells that predicts patient response. 5. Evaluate the effect of JNJ-40340346527 on immune cell populations (cytotoxic T cells, etc.) and phospho-signaling proteins by CyTOF analysis in pre- and post-treatment samples in order to identify biomarkers that predict patient response and prioritize potential combination strategies for future clinical trials. 6. Determine how leukemia cells change in response to CSF-1R inhibition by assessing cells collected pre- and post-treatment using an *ex vivo* sensitivity to a panel of small molecule inhibitors to determine what new drug sensitivities may emerge in AML cells after CSF-1R inhibition.
Number of Participants	Up to 28 participants (14 in each arm) will be enrolled. There will be 7 patients in Stage I and 7 patients in Stage II with the total of 14 patients per arm. Given the expected accrual rate of 14 participants per year, the study is expected to take 36 months (24 months of accrual period and the minimum follow-up of 12 months).
Duration of Therapy	Participants demonstrating favorable response to treatment are eligible to continue additional cycles of study agent until disease progression, death, or investigator discretion.
Duration of Follow Up	Until death or minimum of 12 months follow-up from the last dose of JNJ-40346527.
Inclusion Criteria	1. Ability to understand and the willingness to sign a written informed consent document. 2. Age ≥18 years at time of informed consent. Both men and women and members of all races and ethnic groups will be included. 3. Morphologically documented relapsed/refractory AML as defined by World Health organization (WHO) criteria after at least 1 prior therapy for AML with the exception of hydroxyurea, and not felt to have curative treatment options per treating physician, or the patients themselves are unwilling to consider curative treatment options.

	4. Sufficient and viable bone marrow aspirate or peripheral blood collection to use for the *ex vivo* sensitivity assay. 5. ECOG performance status 0 to 2 (Refer to Appendix A) 6. Women must not be pregnant or breastfeeding. Women of childbearing potential must have a negative serum or urine pregnancy test within 14 days prior to start of study drug administration. 7. Participants must agree to use an adequate method contraception (see Appendix C). 8. Must be able to take oral medications. 9. Adequate organ function as defined by the following: a. Serum creatinine ≤2× the upper limit of normal (ULN), or glomerular filtration rate >20ml/min as calculated by Cockgroft-Gault formula. b. Serum potassium, magnesium, and calcium (corrected for albumin) within institutional normal limits or can be corrected with supplementation. c. Total serum bilirubin ≤2.5× ULN. d. Serum aspartate transaminase (AST) and/or alanine transaminase (ALT) ≤2.5× ULN.
Exclusion Criteria	1. Diagnosis of acute promyelocytic leukemia (APL, or AML M3 subtype) 2. Active central nervous system involvement with AML 3. Concurrent active malignancy with expected survival of less than 1 year. For example, candidates with treated skin cancers, prostate cancer, breast cancer, etc. without metastatic disease are candidates for therapy since their expected survival exceeds that of relapsed or refractory AML. All subjects with concurrent malignancies will be reviewed by the PI prior to enrollment. 4. Clinically significant GVHD or active GVHD requiring initiation or escalation of treatment within 28 day screening period 5. Clinically significant coagulation abnormality, such as disseminated intravascular coagulation. 6. Participants who are currently receiving any other investigational agents. 7. Previous treatment with CSF-1R kinase inhibitor or CSF-1R blocking antibody. 8. Known clinically significant liver disease defined as ongoing drug-induced liver injury, chronic active hepatitis C (HCV), chronic active hepatitis B (HBV), alcoholic liver disease, non-

	alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, portal hypertension, or history of autoimmune hepatitis. Untreated HIV or active hepatitis C detectable by PCR, or chronic hepatitis B (patients positive for hepatitis B core antibody who are receiving IVIG are eligible if HepB PCR is negative). 9. Untreated HIV or active hepatitis C detectable by PCR, or chronic hepatitis B (patients positive for hepatitis B core antibody who are receiving IVIG are eligible if HepB PCR is negative). 10. Known history of cerebrovascular accident, myocardial infarction, or intracranial hemorrhage within 2 months of enrollment. 11. Clinically significant surgery within 2 weeks of enrollment. 12. Per PI discretion, active infection that is not well controlled by antibacterial or antiviral therapy. 13. Cancer-directed therapy within 2 weeks prior to starting treatment, with the exception of hydroxyurea, which is allowed to control white blood cell count. Hydroxyurea will be weaned as soon as clinically feasible. 14. Unwillingness to receive infusion of blood products. 15. Drugs that affect the CYP3A4 systems are allowed and essential for cancer patients, including anti-fungals but should be used with caution. 16. Patients with uncontrolled white blood cell count (defined as >50 K/cu mm not controlled with hydrea).
Investigational Product(s)	JNJ-40346527 will be administered at a dose of 150 mg PO twice daily in continuous 28-day cycles
Statistical Considerations	A Simon 2-stage minimax design will be used to determine clinical efficacy. For each arm, 7 participants will be enrolled in the first stage. If there is at least 1 response among the first 7 participants, the trial will proceed to the second stage and enroll an additional 7 participants. The treatment is considered promising if there are at least 3 responses among 14 participants. The study has 80% power to test the best objective response rate of 5% (poor) vs. 30% (desirable) using one-sided 5% significance level.
Efficacy Assessments	Assess the best objective response rate, duration of response to JNJ-40346527, overall survival and event-free survival in participants with relapsed/refractory AML as stratified by *ex vivo*

	sensitivity.
Safety Assessments	Monitor Grade 3 or higher treatment-related toxicities. Study enrollment will be suspended if the lower 90% confidence interval for Grade 3 or higher treatment-related toxicity exceeds 30% (considered acceptable dose-limiting toxicity (DLT) incidence).

SCHEMATIC OF STUDY DESIGN

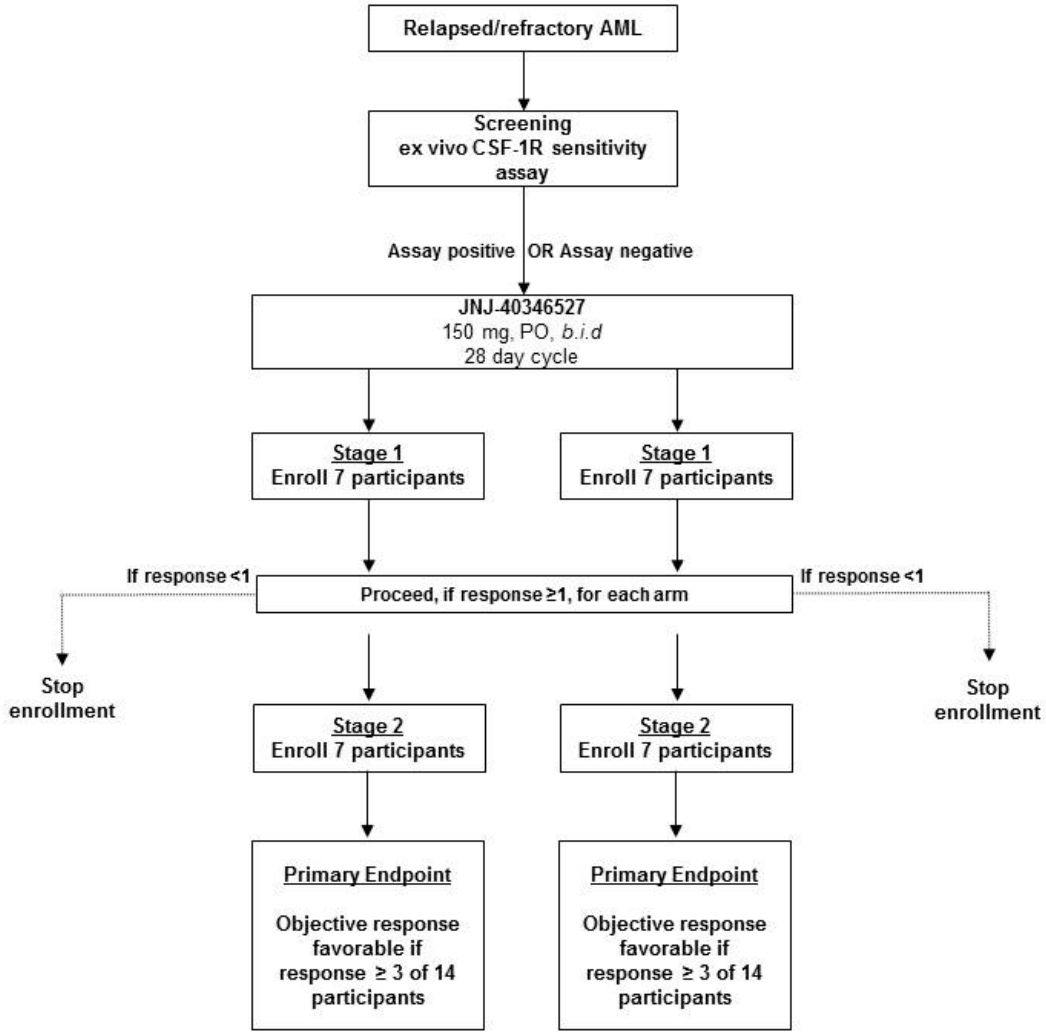

Figure 1. Overview of study design.
Eligible participants with relapsed/refractory AML will undergo bone marrow biopsy and AML cells will be assessed for CSF-1R sensitivity to JNJ-40346527 using an ex vivo drug screening platform. Participants with disease sensitive to JNJ-40346527 in *ex vivo* screening will be assigned to the "*assay positive*" arm. Those deemed insensitive are assigned to the "assay negative" arm. Patients that screen fail the assay will not be included in the study. Patients can rescreen per provider discretion. Both arms will receive the same treatment of JNJ-40346527 (150mg, PO *b.i.d*) over a continuous 28 day cycle. Participants will continue to receive study agent until disease progression. An efficacy stopping rule will halt study enrollment to one or both arms if there is no response among the first 7 participants. Excess toxicity will also suspend enrollment if the incidence of grade 3 or higher treatment-related toxicity significantly exceeds 30%.

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
APL	Acute promyelocytic leukemia
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	Area under the curve
BMA, BMB	Bone marrow aspiration/biopsy
BID/*b.i.d*	Twice daily
BUN	Blood urea nitrogen
CBC	Complete blood cell (count)
CFR	United States Code of Federal Regulations
CK	Creatinine kinase
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CoC	National Institutes of Health (NIH) Certificate of Confidentiality
CR	Complete remission
CRC	Clinical Research Coordinator
CRMS	Clinical research management system
CRQA	Clinical Research Quality & Administration
CRRC	Clinical Research Review Committee (OHSU)
CRF	Case report form
CRMS	Clinical research management system
CSF-1	Colony stimulating factor-1
CSF-1R	Colony stimulating factor-1 receptor
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
CYP	Cytochrome P450
CyTOF	Cytometry by Time of Flight
DFS	Disease-free survival
DLT	Dose limiting toxicity
DOB	Date of birth
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG, EKG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eCRIS	Electronic Clinical Research Information System
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EOT	End of treatment
eq	Equivalent
FACS	Fluorescence-activated cell sorting
FCBP	Female of childbearing potential

FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GVHD	Graft versus host disease
HBeAg	Hepatitis B "e" antigen
HBV	Hepatitis B virus
HCT	Hematocrit
HCV	Hepatitis C virus
HGB	Hemoglobin
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplant
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational device exemption
IL	Interleukin
IND	Investigational new drug application
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IWG	International Working Group
IV	Intravenous
JMD	Juxtamembrane domain
LDH	Lactate dehydrogenase
LFT	Liver function test
M2	mono-oxygenated metabolite
M7	mono-oxygenated metabolite
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MRN	Medical record number
MTD	Maximum tolerated dose
N/A	Not applicable
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
OHRP	Office for Human Research Protections
OHSU	Oregon Health & Science University
ORR	Overall response rate
PCR	Polymerase chain reaction
PD	Progressive Disease
PET	Postitron emission tomography
PD	Pharmacodynamic
P-gp	P-glycoprotein
PHI	Protected health information
PI	Principle Investigator
PK	Pharmacokinetics
PO	*Per os* (by mouth, orally)
PR	Partial remission
PTT	Partial Thromboplastin Time
QD	Per day
QOL	Quality of Life
RBC	Red blood cell (count)

RP2D	Recommended Phase II Dose
RNA	Ribonucleic acid
RNAseq	RNA sequencing
RNI	Reportable new information
RT	Radiation therapy
SAE	Serious adverse event
SD	Stable disease
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
$t_{½}$	Apparent elimination half-life
TAMS	Tumor-associated macrophages
TSMP	Trial Specific Monitoring Plan
UA	Urinalysis
ULN	Upper limit of normal
UP	Unanticipated problem
WBC	White blood cell (count)

1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 OVERVIEW OF RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and other tissues. Accounting for 1.3% of all new cancer cases, AML is the most common type of leukemia in adults. Approximately 21,380 patients will be diagnosed with AML, and an estimated 10,600 AML patient deaths are expected in the United States during 2017.[2] The median age at diagnosis is 67 years, with more than half of individuals are diagnosed 65 years or older. While complete remission rates can be as high as 80% for those undergoing initial induction cytotoxic chemotherapy, the majority of AML patients will ultimately relapse.[3,4] Long-term disease-free survival for relapsed or refractory (RR) AML patients is approximately 30 to 40%, with 3 year overall survival (OS) estimates that do not exceed 10%.[5,6] Several factors are associated with worse outcomes at relapse, including unfavorable cytogenetics at diagnosis, duration of first complete response (CR) less than 12 months, older age, and prior history of hematopoietic stem cell transplant (HSCT).[5,7]

To date, conventional chemotherapy regimens for RR-AML have been unsatisfactory, and while allogeneic HSCT is currently the only viable curative option, only a minority of these patients are eligible for such a treatment approach. Better insight into the genomic and epigenomic landscapes of AML has resulted in numerous attempts to identify more specific, mechanism-driven, targeted therapies.

1.2 COLONY STIMULATING FACTOR-1 RECEPTOR

Colony stimulating factor-1 receptor (CSF-1R), is a 165-kDa, single-pass Type 1 membrane glycoprotein encoded by the c-fms proto-oncogene.[8] CSF-1R acts is the receptor for cognate ligands colony stimulating factor-1 (CSF-1) (also known as macrophage-colony stimulating factor [CSF-1]) and for the interleukin-34 (IL-34) cytokine. CSF-1R is a tyrosine kinase transmembrane receptor composed of an extracellular ligand binding a hydrophobic transmembrane domain, and a cytoplasmic kinase domain.[9]

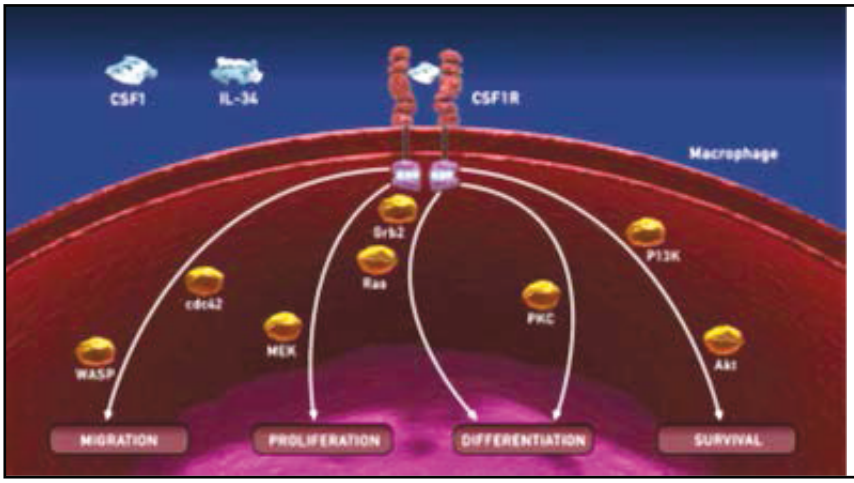

Figure 2. CSF-1R signaling. Signaling through individual phosphor-tyrosine residues within the intracellular CSF-1R tyrosine kinase domain activates specific downstream signaling pathways, thus affecting critical macrophage functions including migration, cytokine expression, proliferation and differentiation of progenitors, as well as survival.
Source: JNJ-40346527 IB 4th ed

Binding of the CSF-1 or IL-34 ligands causes CSF-1R to dimerize and results in the phosphorylation of regulatory tyrosine residues located in the c-terminus. Tyrosine phosphorylation subsequently elicits a downstream signaling cascade through multiple pathways, including phosphatidylinositol-3-kinase (PI3K), protein kinase C (PKC), mitogen-

activated kinase (MEK), and Wiskot-Aldrich syndrome protein (WASP) (**Figure 2. CSF-1R signaling.Figure 2**).[8,10]

"CSF-1R is a member of the platelet-derived growth factor (PDGF) receptor family and is closely related to stem-cell factor receptor (c-Kit) and fms-related tyrosine kinase-3 (FLT-3)/Flk2. CSF-1R is expressed primarily by cells of the macrophage lineage, including monocytes, inflammatory and resident tissue macrophages, dendritic cells, and osteoclasts. The CSF-1/CSF-1R pathway regulates the migration, differentiation, and survival of macrophage precursors.[8"a]

1.2.1 CSF-1/CSF-1R SIGNALING AND CANCER

Continuous inflammation in the tumor microenvironment is a hallmark of cancer and is characterized by the presence of immune cells that interact with tumor cells to influence the initiation, growth, and metastasis of tumors. Specifically, tumor-associated macrophages (TAMs), are often prominent immune cells that orchestrate various factors in the tumor microenvironment, and the CSF-1/CSF-1R pathway is shown to regulate the migration, differentiation, and controls the recruitment, differentiation, and survival of TAMs.

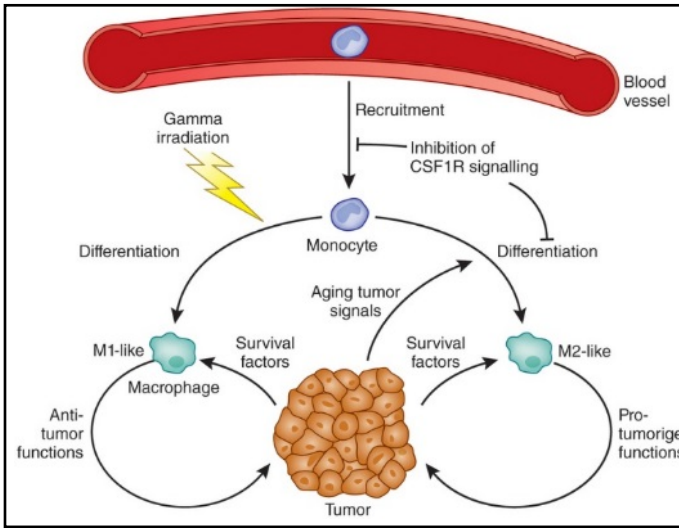

Figure 3. Polarization of tumor associated macrophages.
Cancer cell metabolism, aging, and apoptosis generate signals to attract monocytes from the blood circulation and drive them toward macrophage differentiation into "classical" M1-like and "alternative" M2-like macrophages within the tumor microenvironment. The CSF-1/CSF-1R pathway is involved in the chemotaxis of monocytes into the tumor stroma and the differentiation into immuno-suppressive and tumor-promoting M2-like TAMs.[1]

*"TAMs are generally characterized as being either "classical" M1 macrophages or "alternative" M2 macrophages (**Figure 3**). Classical M1-macrophages are those that interact with T helper 1 [TH1] cells) and are involved in efficient antigen presentation and pathogen killing. Alternatively, M2 macrophages interact with T helper 2 [TH2] cells and demonstrate high phagocytotic and anti-inflammatory activity.[11] In the tumor microenvironment, M1-like TAMs secrete high amounts of pro-inflammatory cytokines and are thought to promote anti-tumor immunity. In contrast, M2-like TAMs produce low amounts of pro-inflammatory cytokines and higher amounts of the anti-inflammatory cytokine IL-10. As such, M2-like TAMs are thought to promote tumor progression by contributing to the resolution of inflammation, stimulating tumor angiogenesis, and suppressing the activity of cytotoxic T cells.[11]*

The precise roles played by the M1- and M2-like TAM phenotypes during tumor progression and in response to anti-tumor therapies are the subject of intense investigations. However, it appears that M1-like TAMs are pre-dominantly present in pre-malignant and early stages of

tumor development, whereas in locally advanced and invasive tumors the presence of inflammatory cytokines, including CSF-1 and metabolic signals (lactic acid and hypoxia), promote TAM polarization toward the M2-like phenotype.[1] These M2-like TAMs overexpress CSF-1R and may be highly dependent on CSF-1; their presence in various solid[12] and hematologic[13] malignancies is of prognostic relevance and correlates with poor survival.

Targeting and depleting TAMs is emerging as an attractive paradigm for novel anti-tumor therapies.[14] The CSF-1/CSF-1R pathway is a particularly attractive molecular target to selectively inhibit the recruitment, activation, polarization, and survival of immunosuppressive TAMs. Multiple clinical drug candidates that target CSF-1R intrinsic tyrosine kinase activity, or interfere with CSF-1 binding, receptor dimerization, or receptor signaling, are currently undergoing clinical development."[a] However, there are no clear biomarkers to identify responsive patients since CSF-1R inhibitors don't directly target cancer cells. Data from an *ex vivo* drug screening platform has found that 20-25% of AML patient samples (leukemia cells and associated surrounding cells) are sensitive to CSF-1R inhibitors[15]. This assay may be a useful biomarker to predict sensitivity to CSF-1R inhibitors. Further study of the sensitive AML patient samples has suggested that CSF-1R indirectly targets supportive cells within the marrow microenvironment, which leads to subsequent loss of pro-growth signals to the leukemia cells. This is similar to the mechanism in tenosynovial giant cell tumors, where CSF-1R inhibits the expansion of associated monocytes to reduce tumor size (see Figure 4). Initial studies have suggested that a subset of CD14 monocytes is likely the target for CSF-1R. That being said, pre-clinical research has not revealed a direct relationship between just the number of CD14 cells and *ex vivo* sensitivity. Data suggests that CD14 monocytes can be activated to secrete paracrine signals to support AML cell growth, but CD14 cells are not necessarily activated in every AML sample, when means there is not a perfect correlation. One of the exploratory goals of the clinical trial will be to more accurately characterize the CD14 supportive cells (using CyTOF) that predict CSF-1R sensitivity. Until the mechanism is better understood, the *ex vivo* sensitivity assay has worked reliably in the lab for many years, and will be used to stratify patients into sensitive and non-sensitive arms to test for response to CSF-1R inhibitors.

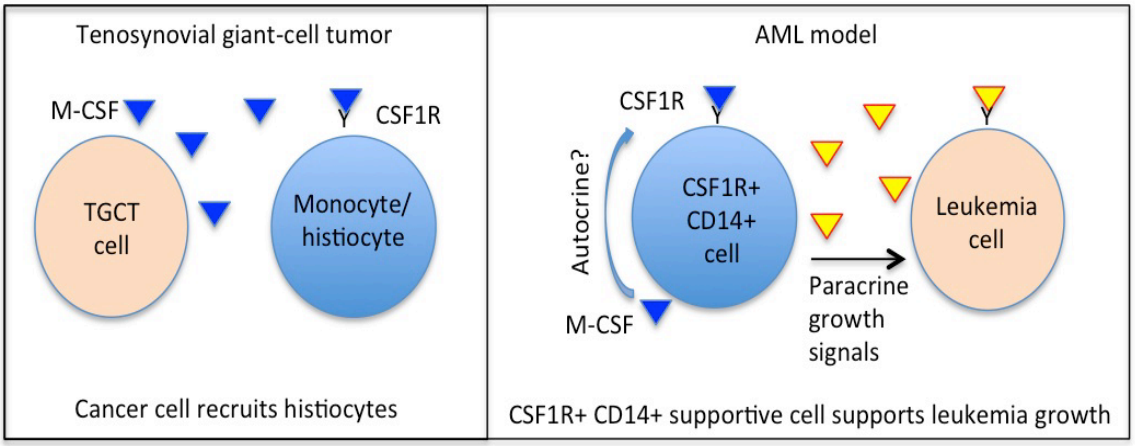

Figure 4. Model of CSF-1R signaling in tenosynovial giant cell tumor (TGCT) and proposed model for AML. In TGCT the tumor cells themselves synthesize and secrete CSF-1 which stimulates growth and expansion of infiltrating monocytes. In AML, we propose that supportive cells expressing CSF-1R are stimulated by CSF-1, perhaps through an autocrine pathway, and then secrete other cytokines and growth signals for AML cells. Inhibition of CSF-1R signaling leads to a reduction in supportive paracrine growth signals and AML cell growth.

1.3 OVERVIEW OF JNJ-40346527

Please refer to investigator brochure for detailed information.[a]

JNJ-40346527 is a potent orally available, small-molecule inhibitor of CSF-1R tyrosine kinase activity that is in clinical development for the treatment of diseases in which macrophages play an important causative role, such as (i) in amplifying chronic inflammation and promoting tissue remodeling in inflammatory diseases or (ii) in stimulating cell growth and in providing suppression of immune-surveillance mechanisms such as those in the microenvironment of some tumors.

1.3.1 MECHANISM OF ACTION FOR JNJ-40346527

"JNJ-40346527 is a selective inhibitor of CSF-1R tyrosine kinase that is capable of inhibiting monocyte and macrophage responses to CSF-1. In vitro kinase assays show that only CSF-1R tyrosine kinase was inhibited >50% at 0.01 µM, whereas other kinases (e.g., FMS-like tyrosine kinase 3 (FLT3), JAK2) were not inhibited at similar concentrations."

1.3.2 PRE-CLINICAL EXPERIENCE

In vivo, JNJ-40346527 demonstrates robust CSF-1R-specific pharmacodynamic (PD) activity in mice and rats, and possesses the ability to reduce macrophage recruitment and differentiation in animal models of inflammatory disease and malignant tumors.[a]

"In mice, the intravenous (IV) administration of recombinant CSF-1 induced c-fos mRNA expression in splenic macrophages. Treatment with JNJ-40346527 at 3 and 10 mg/kg administered 6 hours before IV administration of CSF-1 inhibited c-fos mRNA expression by 75% and 100%, respectively".[a]

"Inhibition of ex vivo CSF-1-mediated CSF-1R phosphorylation of blood cells obtained from healthy rats and from rats with streptococcal cell wall (SCW)-induced arthritis was investigated as a PD biomarker of JNJ-40346527 activity. The IC50 for JNJ-40346527 inhibition of CSF-1-induced CSF-1R phosphorylation ex vivo in blood cells from healthy rats was 20 ng/mL and in blood cells from arthritic rats was 21 ng/mL."[a]

1.3.2.1 *Pharmacokinetics and metabolism*

The pharmacokinetics of JNJ-40346527 has been evaluated in rodents (mice and rat), canine and primate models.[a] *"In all four species tested, single-dose PO administration of JNJ-40346527 was associated with rapid absorption (t_{max} = 1 to 3.3 hours)."*[a] *No sex-related differences in JNJ-40346527 exposure were observed.*

"JNJ-40346527 is highly bound to plasma proteins and liver microsomes and is partitioned into red blood cells. The elimination of JNJ-40346527 is slow with a plasma half-life ranging from a minimum of 7 hours (in rats) to a maximum of 32 hours (in dogs). Following a single IV administration, extensive distribution outside of plasma is detected with the highest JNJ-40346527 concentrations measured in kidney followed by muscle, liver, lung, spleen, heart, and brain.

JNJ-40346527 is a substrate of CYP450 and is primarily metabolized through oxidative biotransformation catalyzed by CYP3A4 leading to the formation of carboxymetabolites. Minor

[a] JNJ-40346527 IB 4th ed - Janssen Confidential Information

pathways are catalyzed by CYP2C8 and CYP2C9 leading to monooxygenated metabolites. Excretion of JNJ-40346527 and its metabolites occurred primarily via feces."[a]

1.3.2.2 *Preclinical toxicities*

*"JNJ-40346527 was evaluated at 10 mg/kg in rats after 3 months of dosing and 25 mg/kg in dogs after 9 months of dosing. In general, pathology findings were mild and reversible after the 1 month recovery period. Relevant toxicities observed with JNJ-40346527 across the species that are considered potentially related to the mode-of-action of CSF-1R inhibition are summarized in **Table 1**".*[a]

Table 1. Summary of preclinical toxicities associated with CSF-1R inhibition[a]

Hematopoietic system:	• Bone marrow hypocellularity with decreased erythropoiesis and increased accumulation of adipose tissue; • Peripheral blood changes with decreased lymphocytes and increased neutrophil counts
Kidney:	• Nephropathy and increased glomerular thickness; • Urinary calcium decrease
Liver:	• Transaminase (AST and ALT) elevations
Blood vessels:	• Fibrinoid necrosis
Connective tissue:	• Mucinous accumulation
Bone:	• Increased thickness of the epiphyseal plate in the femur
Spleen:	• Accumulation of congestion and pigment laden macrophages
Testicles:	• Bilateral degeneration
Skin:	• Sensitizing potential
Eyes:	• Severe irritant

1.3.3 CLINICAL STUDIES OF JNJ-40346527

"Clinical information on the PK/PD, safety, and efficacy of JNJ-40346527 are available for 178 participants that enrolled into 3 completed clinical studies conducted in distinct populations:

- *Phase 1 Study 40346527EDI1001 in healthy volunteers (n = 94)*
- *Phase 2a Study 40346527ARA2001 in subjects with active rheumatoid arthritis (n = 63)*
- *Phase 1/2 Study 40346527HKL1001 in subjects with Hodgkin's lymphoma (n = 21)"*[a]

1.3.3.1 *Pharmacokinetics in Humans*

"The pharmacokinetic characteristics of JNJ-40346527 were assessed in all 3 clinical studies conducted so far. Across studies the following main PK characteristics of JNJ-40346527 following multiple daily oral regimen were observed:

- *Rapid absorption following oral administration*
- *Dose proportional increase of C_{max} (following QD dosing) and AUC (QD and BID dosing)*
- *Mean terminal half-life ($t_{½}$) of ~140 hours*
- *Dose-related systemic accumulation*
- *Steady state level reached by ~21 days of dosing*
- *No apparent sex related differences in PK characteristics*
- *No impact of food on PK characteristics"*[a]

1.3.3.2 *Metabolism in Humans*

"The major JNJ-40346527 metabolite in humans, M7, is generated by mono oxygenation. The formation of M7 is due largely to the CYP2C subfamily, specifically CYP2C8, and CYP2C19. M7 was found to be slightly (<2-fold) more potent than JNJ-40346527 in an in vitro CSF-1R kinase assay. The formation of the other metabolite M2 is largely due to CYP3A4. Radiolabeled studies have not been conducted in humans, however in animals ^{14}C-JNJ-40346527 was highly bound (≥99%) to plasma proteins in all species tested. After 25 mg/kg oral administration of ^{14}C-JNJ-40346527 to male rats and male dogs, radioactivity was excreted primarily in feces."[a]

1.3.3.3 *Drug Interactions*

JNJ-40346527 is a reversible inhibitor of primarily CYP3A4 and CYP2C8 and to a lesser extent of several other CYP isoforms (i.e., CYPs 2B6, 2C9, 2C19, and 2D6) in vitro. JNJ-40346527 increased the plasma exposure of midazolam (by ~65%) in a clinical Phase 1 study, suggesting a weak inhibition of CYP3A4 at clinically relevant doses.

1.3.3.4 *Safety in Humans*

JNJ-40346527 was generally well tolerated by (i) healthy volunteers, (ii) subjects with active RA, and (iii) subjects with relapsed or refractory HL. The most frequent JNJ-40346527 treatment-emergent adverse events (AEs) are shown in **Table 2**. [a]

Table 2. Summary of JNJ-40346527 treatment emergent adverse events[a]

Organ system	Treatment emergent AEs
Gastrointestinal:	• diarrhea, • nausea, • vomiting • constipation, • abdominal pain, • gastroesophageal reflux
Hematologic:	• anemia, • decrease in WBC (neutrophils, monocytes, lymphocytes), • reticulocytes
Hepatic:	• AST and ALT increase
Pulmonary:	• dyspnea
Constitutional symptoms:	• pyrexia, • headache, • back pain
Laboratory changes:	• increase in creatinine kinase and lactate dehydrogenase

1.3.3.5 *Efficacy in Humans*

"The preliminary efficacy of JNJ-40346527 was evaluated in participants with active rheumatoid arthritis in Study 40346527ARA2001. No consistent evidence of efficacy was observed in subjects with RA receiving JNJ-40346527 compared with subjects receiving the placebo.

In study 40346527HKL1001, limited efficacy was observed for JNJ-40346527 evaluated in participants with relapsed or refractory Hodgkin's lymphoma. One out of 20 evaluable subjects (5.0%) demonstrated complete response. An additional 11 subjects (55.0%) experienced stable disease, while 8 subjects (40.0%) had progressive disease."[a]

1.3.4 SMALL MOLECULAR KINASE INHIBITOR SCREEN

The kinase inhibitor screen is an *ex vivo* drug screening platform that facilitates functional evaluation of small molecule inhibitors on primary patient samples.[15] In this assay, a library of small-molecule inhibitors is plated in 384-well format in 7-point concentration series. Primary AML patient specimens are cultured on the assay plates (10,000 cells/well) for 3 days, after which drug sensitivity is assessed by a tetrazolium-based viability assay. A probit dose-response curve is generated for each drug, and IC_{50} values are computed based on the probit models. Effective selection of drugs for patients using this assay has been achieved in numerous n-of-1 studies and within the context of ongoing phase 1b (NCT02779283) and phase 2 (NCT01620216) trials for newly diagnosed and relapsed/refractory AML, respectively.

1.4 **RATIONALE**

CSF-1R inhibitors have caused growth inhibition in 20-25% of AML samples screened with the *ex vivo* assay (in revision). In particular, treatment with the CSF-1R inhibitor JNJ-28312141 has resulted in a sensitivity rate of ~37% (as defined by a sensitivity cutoff of ≤ 40 nM). Response to CSF-1R inhibition does not correlate with intrinsic CSF-1R expression in leukemia cells, but rather appears to be related to CSF-1R expression in a subpopulation of supportive cells that provides paracrine growth signals. Our underlying hypothesis is that JNJ-40346527 targets a subpopulation of supportive cells, which leads to interruption of paracrine survival signals to leukemia cells, and subsequent leukemia cell death. This is similar to the mechanism of action of JNJ-40346527 in tenosynovial giant cell tumor; however, in tenosynovial giant-cell tumors the malignant cell secretes CSF-1, which recruits non-malignant CSF-1R+ monocytes and histiocytes. In our model, the non-malignant CSF-1R$^+$ population is supporting malignant leukemia cell survival by an unknown paracrine signal and this signal is turned off after CSF-1R inhibition.

We hypothesize that the CSF-1R inhibitor JNJ-40346527 will be effective in treating a subset of AML patients, and that given the absence of genetic or other markers, we can select sensitive patients using our *ex vivo* functional screen.

1.4.1 DOSE RATIONALE

Results of study 40346527HKL1001, investigating JNJ-40346527 in patients with relapsed or refractory Hodgkin's lymphoma found optimal inhibition of phosphorylated CSF-1R at 150 mg twice a day.[16] In this study, participants will receive JNJ-40346527 at 150 mg PO twice daily in continuous 28-day cycles.

1.5 **POTENTIAL RISKS AND BENEFITS**

1.5.1 KNOWN POTENTIAL RISKS

Available clinical safety data suggest that JNJ-40346527 is likely to be safe and well tolerated. Based on the mechanism of CSF-1R inhibition, however, there is a risk that JNJ-40346527 may induce side effects when administered as single agent (or in combination with other agents) that have not been observed yet and that may be of severe intensity. Toxicities reported with other CSF-1R targeting small molecules or antibodies that have not yet been reported with JNJ-40346527 include:

1. *FPA008,* a small-molecule CSF-1R inhibitor. Phase 1 study data collected following participant exposure to FPA008 was associated with AEs of eyelid edema, facial swelling,

pruritus, and blurred vision.[17]

2. *PLX3397,* a small-molecule CSF-1R inhibitor. In a Phase 2 study conducted with the *PLX3397*, cases of hair depigmentation and liver toxicity were observed.[18]
3. *Emactuzumab*, a CSF-1R inhibiting antibody. Investigators of a Phase 1 study noted that *Emactuzumab* was associated with cases of lupus erythematosus and cases of cutaneous toxicities, including; erythema, pruritus, dermatitis and facial edema were reported.[19]

1.5.2 KNOWN POTENTIAL BENEFITS

Given the lack of treatment options for treating relapse or refractory AML, the current study may provide access to a new treatment approach not previously available. It cannot, however, be guaranteed that participants in this study will directly benefit from treatment during participation, as the clinical trial is designed to provide information about the safety and effectiveness of the investigational approach.

1.6 CORRELATIVE STUDIES BACKGROUND

The goals of the correlative studies are twofold:

1. Identify the biomarkers that correlate with clinical response, and
2. Identify the effect of JNJ-40346527 on leukemia cells and the immune microenvironment and potential drug combinations for future trials.

The information from the second goal will be important to understand what cells are targeted by CSF-1R inhibition, and identify additional targets for combination trials. For example, removing supportive paracrine CD14$^+$ cells from the leukemia microenvironment may uncover novel kinase inhibitor sensitivities in the leukemia cells that were masked by paracrine survival signals (**Figure 4**). Alternatively, CSF-1R inhibition may enhance expression of immune checkpoint proteins such as PD1 or PDL1 in the leukemia microenvironment, facilitating use of immune checkpoint inhibitors in AML.

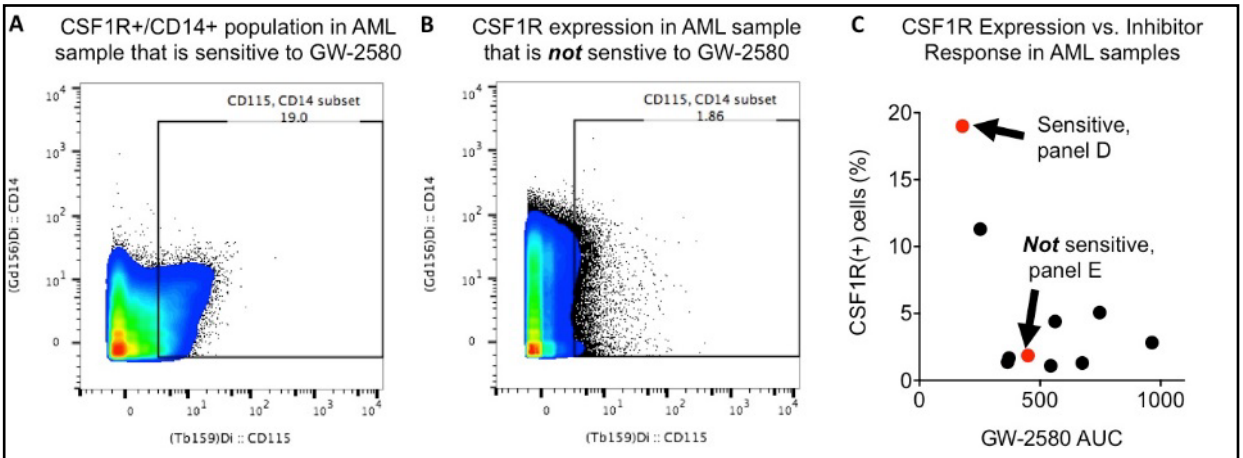

Figure 5. CSF-1R is expressed in non-malignant CD14+ cells.
CSF-1R is expressed in non-malignant CD14+ cells, which correlates with *ex vivo* sensitivity to GW-2580, a highly specific CSF-1R inhibitor. AML samples were analyzed for cells that express CD14 and CSF-1R (CD115) by CyTOF. Samples with **A)** CD14+ CSF-1R+ and **B)** CD14+ CSF-1R- populations are shown. **C)** *Ex vivo* sensitivity and correlation with CSF-1R+ cells is shown,

Specific cell populations in the leukemia immune microenvironment will also likely be modulated by JNJ-40346527, such as T-cell and NK cell populations, which could potentially enhance antibody-dependent cellular cytotoxicity of targeted antibodies such as talacotuzumab (CSL362/JNJ-56022473). Understanding which patients are most likely to respond to JNJ-40346527 treatment, and how the leukemia cells and their immune microenvironment are affected by treatment, will be critical to develop effective combinations in the future.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

Evaluate preliminary efficacy of JNJ-40346527 in participants with relapsed/refractory AML, assessed by best objective response rate (>PR).

2.2 SECONDARY OBJECTIVES

1. Assess the safety of JNJ-40346527 in participants with relapsed or refractory AML.
2. Assess the duration of disease response associated with JNJ-40346527.
3. Overall incidence of treatment-related and non-treatment related toxicity.
4. Duration of response.
5. 12-month event-free survival.
6. 12-month overall survival.

2.3 EXPLORATORY OBJECTIVES

1. Evaluate the pharmacokinetics of JNJ-40346527 and effective inhibition of CSF-1R in marrow aspirates using plasma inhibitory assays, with established CSF-1R-sensitive cell lines.
2. Identify the effect of JNJ-40346527 on leukemia cells and the immune microenvironment.
3. Identify and quantify the specific subpopulation of cells that express CSF-1R in participants and correlate these with clinical response to JNJ-40346527.
4. Analyze the frequency of mutations using genomic DNA from leukemia participants to determine if there is a genetic signature that predicts response to JNJ-40346527.
5. Using RNA sequencing (RNAseq), identify an expression signature in CSF-1R^{+} cells that predicts patient response.
6. Evaluate the effect of JNJ-40346527 on immune cell populations (cytotoxic T cells, etc.) and phospho-signaling proteins by CyTOF analysis in pre- and post-treatment samples in order to identify biomarkers that predict patient response and prioritize potential combination strategies for future clinical trials.
7. Determine how leukemia cells change in response to CSF-1R inhibition by assessing cells collected pre- and post-treatment using an *ex vivo* sensitivity to a panel of small molecule inhibitors to determine what new drug sensitivities may emerge in AML cells after CSF-1R inhibition.

3. STUDY DESIGN AND ENDPOINTS

3.1 DESCRIPTION OF THE STUDY DESIGN

Refer to Section 10*, STATISTICAL CONSIDERATIONS for additional information regarding statistical methods used in this study.*

This is a Phase 2, Simon 2-stage minimax design to determine clinical efficacy of JNJ-40346527 in relapsed/refractory AML. Participants must meet the inclusion criteria, have none of the exclusion criteria, and have provided written informed consent before the conduct of any screening tests not performed routinely in their treatment.

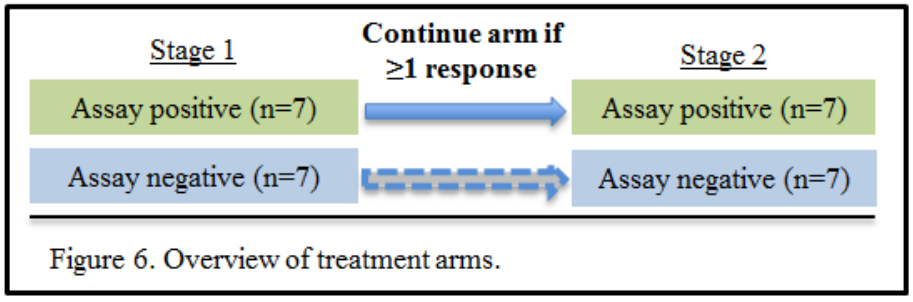

Figure 6. Overview of treatment arms.

Results from preclinical studies suggest that responsive patients may be selected by using an *ex vivo* assay with JNJ-40346527. Eligible participants will be divided into two treatment arms based on an *ex vivo* sensitivity of AML cells derived from either bone marrow aspirates or peripheral blood (if inaspirable and ≥20% circulating blasts). Participants with an *ex vivo* IC_{50} that is ≤20% of the median IC_{50} (to be determined with preclinical testing) will be considered sensitive to JNJ-40346527 (termed "assay positive"), whereas those with an IC_{50} >20% of the median IC_{50} will be considered insensitive (termed "assay negative") for purposes of assignment. This threshold is set prior to the study start and does not change. This will result in 2 study arms: 1) Assay positive and 2) Assay negative (Figure 6). Patients that screen fail (for example indeterminate assay results or insufficient sample) will not be included in the study. Patients can rescreen per provider discretion.

For each arm, 7 participants will be enrolled in the first stage. If there is at least 1 response among the first 7 participants, the study will proceed to the second stage, in which an additional 7 participants will be enrolled. The treatment is considered promising if there are at least 3 responses among 14 participants. The best objective response and exact confidence intervals will be estimated using the binomial distribution for each arm.

We anticipate that *ex vivo* sensitivity will predict participants' response and that only the assay positive arm will continue to enroll in stage 2. The expected total enrollment of both Arms would be 21 participants in this case. If no participant responds in either treatment arm, the enrollment will end with 14 patients. If ≥1 out of 7 eligible participants respond to JNJ-40346527 in both the assay positive and assay negative arms, then both arms will continue to stage 2. In this case, the maximum enrollment would be 28 participants.

This study has a stopping rule for both futility (a lack of efficacy) and safety. No response among the first 7 patients is defined as futility and will halt each either arm of the study.

Likewise, excess toxicity will suspend enrollment if the lower 90% confidence interval for Grade 3 or higher treatment-related toxicity exceeds 30% (considered acceptable dose-limiting toxicity (DLT) incidence).

3.2 **STUDY ENDPOINTS**

3.2.1 PRIMARY ENDPOINT

Endpoint	**Start**	**End**
1. Best objective response rate.	First dose of JNJ-40346527	Over 3 cycles

3.2.2 SECONDARY ENDPOINT(S)

Endpoint	**Start**	**End**
1. Overall incidence of treatment-related and non-treatment related toxicity..	First dose of JNJ-40346527	30 days after last dose of study agent
2. Duration of response. For patients that achieve ≥PR, how long do they maintain this response before progression.		
3. Event-free survival at 12-months		12 months from first dose
4. Overall survival at 12-months		Death (or date of last contact)

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1 PARTICIPANT INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Ability to understand and the willingness to sign a written informed consent document.
2. Age ≥18 years at time of informed consent. Both men and women and members of all races and ethnic groups will be included.
3. Morphologically documented relapsed/refractory AML as defined by World Health organization (WHO) criteria after at least 1 prior therapy for AML with the exception of hydroxyurea, and not felt to have curative treatment options per treating physician, or the patients themselves are unwilling to consider curative treatment options.
4. Sufficient and viable bone marrow aspirate or peripheral blood collection to use for the *ex vivo* sensitivity assay.
5. ECOG performance status 0 to 2 (Refer to Appendix A)
6. Women must not be pregnant or breastfeeding. Women of childbearing potential must have a negative serum or urine pregnancy test within 14 days prior to start of study drug administration.
7. Participants must agree to use an adequate method contraception (see Appendix C).
8. Must be able to take oral medications.
9. Adequate organ function as defined by the following:
    a. Serum creatinine ≤2× the upper limit of normal (ULN), or glomerular filtration rate >20ml/min as calculated by Cockgroft-Gault formula.
    b. Serum potassium, magnesium, and calcium (corrected for albumin) within institutional normal limits or can be corrected with supplementation.
    c. Total serum bilirubin ≤2.5× ULN.
    d. Serum aspartate transaminase (AST) and/or alanine transaminase (ALT) ≤2.5× ULN.

4.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Diagnosis of acute promyelocytic leukemia (APL, or AML M3 subtype)
2. Active central nervous system involvement with AML
3. Concurrent active malignancy with expected survival of less than 1 year. For example, candidates with treated skin cancers, prostate cancer, breast cancer, etc. without metastatic disease are candidates for therapy since their expected survival exceeds that of relapsed or refractory AML. All subjects with concurrent malignancies will be reviewed by the PI prior to enrollment.
4. Clinically significant GVHD or active GVHD requiring initiation or escalation of treatment within 28 day screening period.

5. Clinically significant coagulation abnormality, such as disseminated intravascular coagulation.
6. Participants who are currently receiving any other investigational agents.
7. Previous treatment with CSF-1R kinase inhibitor or CSF-1R blocking antibody.
8. Known clinically significant liver disease defined as ongoing drug-induced liver injury, chronic active hepatitis C (HCV), chronic active hepatitis B (HBV), alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, portal hypertension, or history of autoimmune hepatitis.
9. Untreated HIV or active hepatitis C detectable by PCR, or chronic hepatitis B (patients positive for hepatitis B core antibody who are receiving IVIG are eligible if HepB PCR is negative).
10. Known history of cerebrovascular accident, myocardial infarction, or intracranial hemorrhage within 2 months of enrollment.
11. Clinically significant surgery within 2 weeks of enrollment.
12. Per PI discretion, active infection that is not well controlled by antibacterial or antiviral therapy.
13. Cancer-directed therapy within 2 weeks prior to starting treatment, with the exception of hydroxyurea, which is allowed to control white blood cell count. Hydroxyurea will weaned as soon as clinically feasible.
14. Unwillingness to receive infusion of blood products.
15. Drugs that affect the CYP3A4 systems are allowed and essential for cancer patients, including anti-fungals but should be used with caution.
16. Patients with uncontrolled white blood cell count (defined as >50 K/cu mm not controlled with hydrea).

4.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants for this study will be recruited from within the hematology and oncology practices participating research sites. Participants may be identified and referred to this study by their primary treating physician from the outside community. Participants may also initiate contact with the investigator through information of this study posted on the clinicaltrials.gov website.

4.3.1 ACCRUAL ESTIMATES

The number of participants to be accrued is driven by the study primary objective. An estimated 28 participants across OHSU and 2 participating sites will be recruited over a 24 month period.

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No participant will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied. Gender-nonconforming and gender-fluid individuals as members of the general population will also be recruited.

The projected gender, racial, and ethnic composition of the study will represent that of the state of Oregon (**Table 3**).

Table 3. Projected accrual for present study based on Oregon population demographics

Ethnic Category	Sex/Gender					
	Females		Males		Total	
	n	%	n	%	n	%
Hispanic or Latino	2	6.4	2	6.3	4	12.7
Not Hispanic or Latino	11	38.7	11	37.9	21	76.6
Ethnic Category: Total of all participants*	13		13			100*
Racial Category						
American Indian or Alaskan Native	1	3.9	1	3.9	2	7.8
Asian	1	2.2	1	2.2	1	4.4
Black or African American	0	1.1	0	1.0	1	2.1
Native Hawaiian or other Pacific Islander	0	0.2	0	0.2	0	0.4
White	12	44.2	12	43.4	25	87.6
Two or more races	1	1.9	1	1.8	1	3.7
Racial Category: Total of all participants*	15	50.5	15	49.5		100

Source: Adapted from U.S. Census Bureau, 2010.
*Totals may not equal 100 due to rounding.

4.3.2 INCLUSION OF CHILDREN

This protocol does not include children because no dosing or adverse event data are currently available on the use of this study agent in this way in persons <18 years of age; therefore, children are excluded from this study.

4.4 REGISTRATION PROCEDURES

4.4.1 PARTICIPANT REGISTRATION

4.4.1.1 *OHSU Registration*

This is a Phase II trial and there is no randomization.

Participants will be required to give written informed consent to participate in the study before any screening tests or evaluations are conducted that are not part of standard care.

Registration from all consented participants must be entered into the OHSU electronic Clinical Research Management System (CRMS, e.g., eCRIS). At a minimum, registration of OHSU participants will include:

- A completed Participant Registration Form
- A completed Eligibility Checklist signed by the Investigator
- Signed copies of the most recently IRB-approved, informed consent form and HIPAA

authorization

4.4.2 MULTICENTER REGISTRATION

The OHSU coordinating center study team will manage the participant registration process. Investigators, or study team designee, at participating sites will identify eligible participants and send source documents that support eligibility to OHSU for review and verification before the participating site may enroll and treat the participant.

The OHSU coordinating center team is responsible for verifying completeness of documents, entering registration information into the Knight CRMS, and assigning a study number/identifier for each individual participant. The OHSU coordinating center will send an email to the participating site to indicate whether or not a participant is eligible and will assign a participant number/identifier.

Registration at participating research site will include a minimum of the following:

- A completed Participant Enrollment Form
- A completed Eligibility Checklist signed by the Investigator
- De-identified source documentation of eligibility
- Signed copies of the most recently local IRB-approved, informed consent form and HIPAA authorization.

Each participating research site is expected to maintain a screening log of all participants who are approached for the study. The log documents an explanation for exclusion due to screen failure. This log should be submitted to the OHSU coordinating center on a regular basis. Participating sites are required to retain, in a confidential manner, sufficient information on each participant so that the participant may be contacted should the need arise

4.5 **PARTICIPANT SCREENING AND ENROLLMENT**

In order to participate in this study, signed informed consent must be obtained from the participant or the participant's legally acceptable representative. The current Institutional Review Board (IRB) approved informed consent must be signed and dated by each participant prior to undergoing any study procedures or before any prohibited medications are withheld from the participant in order to participate in this study.

This study consists of a 28 day screening period. Screening will begin once the participant has provided written informed consent to participate in the study and ends on Day 0 of the study. All screening and baseline evaluations will be performed during the screening phase. Eligible participant assignment to one of two treatment arms, *assay positive* or *assay negative*, based on results from *ex vivo* screening assay will occur no later than 14 days prior to starting treatment with study agent. Samples will be collected from study eligible participants no later than 14 days prior to initiating treatment with study agent. Day 1 of the clinical trial will be when participants are started on JNJ-40346527. Total accrual of all participants is anticipated to take a total of 24 months.

4.6 **PARTICIPANT WITHDRAWAL OR DISCONTINUATION**

Participants are free to withdraw consent and discontinue participation in the study at any time and without prejudice to further treatment. If a participant no longer wants to receive investigational product, but is willing to come for follow-up appointments, the participant's

request should be honored, if possible. The following are examples demonstrating why a participant's treatment might be discontinued.

- Toxicity precludes further study treatment.
- There is a need for any treatment not allowed by the protocol.
- The participant fails to meet the criteria for study treatment.
- Disease recurrence or progression.
- Investigator's discretion.

No further participant contact should be made if the participant withdraws consent for participation in the study. Information about the reason(s) for discontinuation and collection of any new or ongoing adverse events (AEs) should be collected at the time the participant withdraws consent.

For all other reasons for discontinuation from the study treatment phase, the participant should return to the clinic for the end of treatment (EOT) visit according to Section 7.

4.6.1 HANDLING PARTICIPANT WITHDRAWAL AND DISCONTINUATION

Participants that discontinue the first cycle without experiencing a DLT may be replaced. Participants may be replaced if they voluntarily withdraw from the protocol, or if the participant is taken off study per the PI's discretion for reasons such as continued noncompliance. Per 45 CFR 46, the reasons for withdrawal, if known, will be recorded.

4.7 **OFF-STUDY CRITERIA**

Criteria that can take a participant off-study include:

- Participant requests to be withdrawn from study without further follow-up,
- Completed study follow-up period,
- Death,
- Screen failure

4.7.1 SCREEN FAILURE

Any participant that has signed the consent form (for either screening or study participation) but does not meet the study eligibility criteria, or meets study eligibility criteria but terminates the participation prior to receiving study treatment, will be considered a screen failure. The reason for screen failure should be captured in the database for each participant failing to meet the eligibility criteria.

4.8 **STUDY DISCONTINUATION**

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Manufacturer, Sponsor, local IRB or other regulatory agency. If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Reasons for terminating the study may include the following:

- Incidence or severity of adverse events, in this or other studies, indicates a potential health hazard to participants.

- Interim futility analysis demonstrates that the primary endpoint is unlikely to be met.
- Data that are not sufficiently complete and/or evaluable.
- Investigator(s) do not adhere to the study protocol, or applicable regulatory guidelines in conducting the study.
- Participant enrollment is unsatisfactory.
- Submission of knowingly false information from the study site to Sponsor or regulatory authorities.
- Upon instruction by local or other regulatory, or oversight authority.

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the Sponsor, IRB and/or FDA.

5. INVESTIGATIONAL PRODUCT

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 9.4.

5.1 **JNJ-40346527**

"JNJ-40346527 is a selective inhibitor of CSF-1R tyrosine kinase, with an IC_{50} of 0.0032 µM. In tissue culture, concentrations of JNJ-40346527 <10 nM are capable of inhibiting monocyte and macrophage responses to CSF-1. JNJ-40346527 is a hydrochloride salt and has a molecular weight of 498.06 and a molecular formula of $C_{27}H_{35}N_5O_2$●HCl. Refer to investigator brochure for additional details."[a]

5.1.1 ACQUISITION

JNJ-40346527 will be supplied by Manufacturer to the drug distributor Biologics, and prepared by OHSU research pharmacy per manufacturer instructions. Following submission and approval of the required regulatory documents, a supply of JNJ-40346527 may be ordered from Janssen by completing a Drug Request Form.

Allow 4 business days for shipment of drug from receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. There will be no weekend or holiday delivery of drugs.

5.1.1.1 *Re-Supply*

Drug re-supply request form should be submitted electronically to Biologics no less than 4 business days before the expected delivery date. Deliveries will be made Tuesday through Friday. When assessing need for resupply, the institution should keep in mind that shipments may take 4 business days from time of receipt request. JNJ-40346527 is not patient specific. The investigator or designated study staff is responsible for verifying with research pharmacy the existing stock of study agent to assure optimal use of available drug.

5.1.2 FORMULATION, APPEARANCE, PACKAGING AND LABELING

"JNJ-40346527 drug substance is a white to off-white powder. The active JNJ-40346527 is available as free-base equivalent (eq.) 50 mg and 150 mg hard gelatin capsules. Both capsules are sized 00 opaque capsule. Qualitatively, the hard gelatin capsule contains JNJ-40346527, Microcrystalline Cellulose (filler), Lactose Monohydrate (filler), Hydroxypropyl Methylcellulose (binder), Crospovidone (disintegrant)."

All packages containing investigational product will have the following, or similar, language: "Caution: New Drug—Limited by Federal law to investigational use."

5.1.3 PRODUCT STORAGE AND STABILITY

JNJ-40346527 capsules should be stored at room temperature, 15°C to 30°C (59°F to 86°F).

5.1.4 COMPATIBILITY

"JNJ-40346527 is a reversible inhibitor of primarily CYP3A4 and CYP2C8 and to a lesser extent of several other CYP isoforms (ie, CYPs 2B6, 2C9, 2C19, and 2D6) in vitro. JNJ-40346527 increased the plasma exposure of midazolam (by ~65%) in a clinical Phase 1 study, suggesting

a weak inhibition of CYP3A4 at clinically relevant doses.

JNJ-40346527 is an inhibitor of P-gp mediated transport of digoxin in vitro but was not a substrate for P-gp in vitro. Care should be taken if JNJ-40346527 is to be administered with P-gp substrates, especially those with narrow therapeutic index. The clinical impact of co-administration of JNJ-40346527 with known inhibitors and inducers of CYP3A4/5, CYP2C8, or CYP2C19 are not fully understood. An increase or decrease of the systemic exposures of JNJ-40346527 and its active metabolites has to be anticipated" [a]

5.1.4.1 *Solubility*

Very lightly soluble in: 0.1 N HCl, 0.1 N NaOH

Practically insoluble in: H_2O, Citrate/HCl buffer (pH 2-4), Citrate/NaOH buffer (pH 6), Borate/HCl buffer (pH 8), Borate/NaOH buffer (pH 10), simulated intestinal fluid, 20% hydroxypropyl-β-cyclodextrin.

5.1.5 HANDLING

JNJ-40346527 must be dispensed only by the investigator or assigned designee, (e.g., study pharmacist, research nursing staff) to ensure the proper number of capsules are made available to the participants to satisfy dosing requirements for the study. The containers provided to the participant should be labeled with proper instructions for use. The lot numbers, dosing start dates and the number of capsules for each dosage strength must be recorded on the drug accountability pages of record.

5.1.6 PREPARATION

JNJ-40346527 is packaged as hard gelatin capsules. No additional preparation is required.

5.1.7 ADMINISTRATION

JNJ-40346527 will be supplied by Janssen Research & Development, LLC. or its designee in the form of 50 mg and 150 mg hard gelatin capsules as individual participant supply packaged in bottles. JNJ-40346527 is to be taken orally, twice daily. JNJ-40346527 must be taken as follows:

- Participants should be instructed to take the JNJ-40346527 capsules with a large glass of water (~250ml) at the same time each day.
- Participants should be instructed to swallow the JNJ-40346527 capsules whole and not to chew, crush or open them.
- JNJ-40346527 can be taken without regard to meals, preferably right after breakfast and dinner. Anti-acids may affect absorption, suggest adding to use them only 2 hours or more before or after any doses of study drug.
- Regardless, dietary habits around the time of dosing should be as consistent as possible throughout the study, and in particular during those periods when samples are being taken for PK analysis.
- If vomiting occurs during the course of treatment, no re-dosing of the participant is allowed before the next scheduled dose.
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.

- Participants must avoid consumption of grapefruit, grapefruit hybrids, pummelos, star-fruit, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medication, due to potential CYP3A4 interaction with the study medication. Orange juice is allowed.
- Due to potential interactions with JNJ-40346527, no herbal or dietary supplements are permitted, including St. John's Wort without provider consultation.
- Multivitamins are allowed.
- Refer to Appendix C for tables of prohibited medications and medications to be used with caution in association with administration of JNJ-40346527.
- If a subject is taking frequent antacids, e.g. always take JNJ-40346527 with food, ie, within approximately 30 minutes after breakfast in the morning and within approximately 30 minutes after their evening meal.

5.1.8 SPECIAL CONSIDERATIONS FOR ADMINISTRATION

5.1.8.1 *Participant self-administration*

JNJ-40346527 may be self-administered by participant. Specific instructions for at-home administration of JNJ-40346527 must be given to participant by physician or other designated healthcare provider.

5.1.8.2 *Participant Medical Diary*

Participants are required to keep a medical diary to record ingestion of study agent (e.g., frequency, volume of water per ingestion, as well as duration between meals).

5.1.9 ACCOUNTABILITY

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of the study agent. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or 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 or other oversight bodies.

The Investigator or designee will collect and retain all used, unused, and partially used containers of study medication until full accounting has been completed. The Investigator or designee must maintain records that document:

- Investigational product delivery to the study site.
- The inventory at the site.
- Use by each participant including pill/unit counts from each supply dispensed.
- Return of investigational product to the Investigator or designee.
- Destruction or return of investigational product for final disposal.

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study participants.

The investigational product must be used only in accordance with the protocol. The Investigator will also maintain records adequately documenting that the participants were provided the correct study medication specified.

Completed accountability records will be archived by the site. At the completion of the study, the Investigator or designee will oversee shipment of any remaining study drug back to the Manufacturer for destruction according to institutional standard operating procedures. If local procedures mandate site destruction of investigational supply, prior written approval must be obtained from Manufacturer.

5.1.10 DESTRUCTION AND RETURN

At the end of the study, or earlier upon approval from study management, unused supplies of JNJ-40346527 should be destroyed according to institutional policies. Drug supplies will be counted and reconciled in full at the site with all monitoring procedures complete before destruction. Destruction will be documented in the Drug Accountability Record Form.

6. TREATMENT PLAN

6.1 DOSAGE AND ADMINISTRATION

JNJ-40346527 will be administered at a fixed dose of 150 mg PO twice daily in continuous 28 day cycles (defined as a single treatment cycle). Treatment will be administered on an out-patient basis. Reported adverse events and potential risks are described in Section 9. Appropriate dose modifications are described in Section 6.2. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Regimen Description				
Agent	*Premedication; Precautions*	*Dose*	*Route*	*Cycle Length*
JNJ-40346527		150 mg, *b.i.d*	PO	28 Days

6.2 DOSING DELAYS AND MODIFICATIONS

6.2.1 DEFINITION OF DOSE-LIMITING TOXICITY (DLT)

A DLT is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications. A DLT requires a definite, probable or possible adverse experience to be related to the investigational product. Toxicities will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5).
Safety will be assessed by evaluating the incidence of DLTs that exceeds the expected toxicities associated with JNJ-40346527. That is, DLTs are defined as any ≥ Grade 3 treatment related toxicity according to CTCAE v5.0. The following expected adverse events are excluded:

- Grade 3 and 4 prolonged hematologic toxicities
- Grade 3 AST levels (i.e., >5 to 20 x ULN)
- Grade 3 Creatinine kinase (CK) levels (i.e., >3.0 baseline; >3.0 - 6.0 x ULN)

A DLT will also be defined as:

(1) An ANC that fails to recover to >0.5 Gi/L within 42 days from the start of therapy in the absence of active leukemia or myelodysplasia; and,
(2) A platelet count that fails to recover to >20 Gi/L within 42 days from the start of therapy in the absence of active leukemia or myelodysplasia or that is associated with clinically significant bleeding that requires transfusion of red cells or platelets.

6.2.1.1 *Duration of DLT assessment*

The DLT evaluation period will begin with the first dose of JNJ-40346527 and be continuously assessed throughout the study.

6.2.2 DOSE DELAYS

Treatment may be delayed for up to 28 days from the end of a previous 28-day cycle for SAEs described in Table 4. In case of a treatment delay subsequent study assessment days will be adjusted accordingly.

6.2.3 DOSE ESCALATION

No dose escalation is allowed. JNJ-40342527 will be administered at a fixed dose of 150mg twice daily.

6.2.4 DOSE DE-ESCALATION

Dose reductions are allowable per PI discretion. If treatment-related toxicities are observed that based on the investigator's best clinical judgement require a dose reduction, the dose of JNJ-40346527 can be reduced to 100 mg PO BID. The dose of JNJ-40346527 can be reduced only once. In case of another episode of treatment-related toxicity which based on the investigator's best clinical judgement requires a dose reduction, the study treatment with JNJ-40346527 needs to be discontinued.

6.2.5 GENERAL DOSE DELAY GUIDELINES

Dose delays will be made as indicated in **Table 4**. The descriptions and grading scales found in the revised CTCAE v5 will be utilized for dose delays.

Table 4. Dose delay guidelines and management of next dose forJNJ-40346527

Non-hematologic	
≤Grade 1	No dose modification.
Grade 2	No dose modification.
Grades 3-4 and clinically significant*	Dose modification per PI discretion.
Hematologic	
All grades	Dose modification per PI discretion.

*For non-hematologic grade 3 and 4 AEs, JNJ-40346527 will be held until toxicity resolves to grade <2. Once grade <2, JNJ-40346527 will be restarted at 50 mg BID, then increased to 100 mg BID, and finally to 150 mg BID if subject was felt to be deriving clinical benefit and would like to continue on study. This dose escalation regimen will be reviewed by the treating physician and medical monitor.

6.3 TREATMENT PERIOD AND MAINTENANCE

Participants will receive JNJ-40346527 at 150 mg PO twice daily in continuous 28-day cycles. Initial response will be assessed by bone marrow biopsy after cycles 1-3 and then every 3 months thereafter. Further study assessments will be performed as outlined in the Section 7.10, Schedule of Events .

Treatment with JNJ-40346527 will continue until disease progression or stopping rules are triggered as a result of either excess toxicity or lack of efficacy (refer to Section 10.2.4).

Disease progression will be defined as any patient with response ≥ PR who then loses PR based upon the original pre-treatment marrow sample (PR defined as ≥ 50% decrease in marrow blasts to 5-25% of marrow). For example, a patient with 30% blasts on pre-treatment

marrow who achieved CR with 4% blasts and then was found to have 6% blasts with continued hematologic recovery on subsequent marrow (PR) would remain on trial until subsequent marrow blasts were >15%, or with loss of hematologic response. Patients with stable disease who continue to receive clinical benefit per PI review may remain on study drug.

If a participant achieves a complete remission (CR) and is deemed a candidate for allogeneic stem-cell transplant, JNJ-40346527 should be discontinued 7 days before initiation of the conditioning regimen. Treatment with JNJ-40346527 may be resumed 30-100 days after the transplant if patients has a relapse of their disease, no active GVHD, and after review by the PI.

6.4 CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

Supportive measures for optimal medical care are to be given throughout the study as indicated by the treating physician's assessment of the participant's medical need and institutional and general medical guidelines for the care of participants undergoing treatment of AML.

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheals are allowed in general. The participant must be told to notify the investigational site about any new medications begun after the start of the study treatment. All medications (other than investigational products) and significant non-drug therapies (including vitamins, herbal medications, physical therapy and blood transfusions) administered during the study must be listed on the CRF.

6.4.1 BLOOD PRODUCTS

All blood products are to be irradiated and leukocyte-reduced according to institution guidelines. Additionally, cytomegalovirus (CMV)-negative participants should receive CMV-negative blood products according to institution guidelines.

Medications that inhibit Platelet Function and Anticoagulants: Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants. Participants enrolled in this study should not take concomitant medications which durably inhibit platelet function unless medically necessary and caution should be used if anticoagulation is required. For such medications, a wash-out period of 7 days is required prior to starting kinase inhibitor therapy. Agents that inhibit platelet function transiently or inhibit coagulation by other mechanisms are restricted; however, if anticoagulation is required while on study this must first be reviewed with the pharmacist and the study PI.

Medications that directly and durably inhibit platelet function include: Aspirin or aspirin-containing combinations, clopidogrel, dipyridamole, tirofiban, epoprostenol, eptifibatide, cilostazol, abciximab, ticlopidine.

Medications that directly and durably inhibit anticoagulation include: Warfarin, heparin/low molecular weight heparin [e.g., danaparoid, dalteparin, tinzaparin, enoxaparin] exceptions are low-dose warfarin for prophylaxis to prevent catheter thrombosis and heparin for flushes of IV lines.

6.4.2 INFECTION PROPHYLAXIS

The use of prophylactic antibacterial, antifungal, and antiviral agents is recommended according

to institutional guidelines.
Note, certain antibiotics may have interactions with specific inhibitors and thus this must be reviewed closely prior to study enrollment and while on study.

Possible prophylaxis includes use of prophylaxis for HSV infection with acyclovir or valacyclovir; levofloxacin for bacterial prophylaxis, as long as patient is not febrile.

The azole isavuconazole can likely be used concurrently with the study drug without dose adjustments. However if other azoles are prescribed such asposaconazole, fluconazole,or voriconazole, caution must be used as prophylaxis and may require measurement of drug levels to monitor dose. Potential interaction of antifungals should be reviewed with an oncology pharmacist and the study PI.

6.4.3 TREATMENT OF FEVER AND NEUTROPENIA

Neutropenic fever (defined as ANC <0.500/mm^3 or 1.000/mm^3 and known to be falling and temperature ≥38.0ºC) will be treated per institution guidelines.

6.4.4 CYTOCHROME (CYP) INHIBITION

"JNJ-40346527 is a reversible inhibitor of primarily CYP3A4 and CYP2C8 and to a lesser extent of several other CYP isoforms (i.e., CYPs 2B6, 2C9, 2C19, and 2D6) in vitro. JNJ-40346527 increased the plasma exposure of midazolam (by ~65%) in a clinical Phase 1 study, suggesting a weak inhibition of CYP3A4 at clinically relevant doses. The clinical impact of co-administration of JNJ-40346527 with known inhibitors and inducers of CYP3A4/5, CYP2C8, or CYP2C19 are not fully understood. An increase or decrease of the systemic exposures of JNJ-40346527 and its active metabolites has to be anticipated." [a]

"Drugs that induce CYP3A4 activity may decrease JNJ-40346527 plasma concentrations. For participant in which CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be used (Refer to Appendix B for detailed list of agents).

JNJ-40346527 is a substrate of CYP450 and is primarily metabolized through oxidative biotransformation catalyzed by CYP3A4 leading to the formation of carboxymetabolites. Minor pathways are catalyzed by CYP2C8 and CYP2C9 leading to monooxygenated metabolites. Concomitant use of JNJ-40346527 and drugs that inhibit CYP3A4 may increase exposure to certain kinase inhibitors. Caution is warranted when administering JNJ-40346527 to participants taking drugs that are highly dependent on CYP3A4 for metabolism and have a narrow therapeutic index. Systemic exposures to these medications could be increased while receiving JNJ-40346527.

Additionally, strong to moderate CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin) may significantly increase concentrations of JNJ-40346527 and should be used with caution when administered concurrently with JNJ-40346527." [a]

6.4.5 P-GLYCOPROTEINS (P-GP)

"JNJ-40346527 is an inhibitor of P-gp mediated transport of digoxin in vitro but was not a substrate for P-gp in vitro. Care should be taken if JNJ-40346527 is to be administered with P-

gp substrates" especially those with narrow therapeutic index (e.g., digoxin) and consultation with oncology pharmacist and Investigator is required (Refer to Appendix B for detailed list of agents).

6.4.6 GASTROINTESTINAL

Anti-emetics, anti-diarrheal agents and acid suppressive therapies should not be taken 2 hours before or after study drug (e.g., antacids, H2 blockers, and proton pump inhibitors) will be prescribed per institutional guidelines.

Study participants may receive anti-emetic therapy as needed during their treatment which may include ondansetron, prochlorperazine, haloperidol and lorazepam.

The use of anti-diarrheals will be administered per investigator's discretion. First line agents such as loperamide and tincture of opium, and/or octreotide can be utilized.

Nonclinical data demonstrates that JNJ-40346527 was not affected by the concomitant intake of medications inducing a pronounced and long-lasting reduction of gastric acid production such as proton-pump inhibitors or histamine H2 receptor antagonists. The use of acid reducing agents will be per investigators discretion.

6.5 **PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES**

6.5.1 GENERAL PRECAUTIONS

JNJ-40346527 is an investigational drug. All subjects receiving JNJ-40346527 should be closely monitored according to the relevant clinical study protocol. While there has not been increased incidence of infection-related AEs observed, investigators should be vigilant for serious infections since JNJ-40346527 may impact subject's ability to fight infection via a reduction in macrophage function.

6.5.2 ANTIGENICITY AND MUTAGENICITY

There is no information on the risk of antibody formation against JNJ-40346527. JNJ-40346527 is not considered genotoxic based on the currently available in vitro and in vivo data.

6.5.3 IMPAIRMENT OF FERTILITY AND PREGNANCY

Since no fertility studies have been performed to date; it is possible that JNJ-40346527 may elicit embryofetal toxicity. JNJ-40346527 can only be administered in female and male subjects who practice effective birth control methods (refer to Appendix C) for 120 days after their last dose. For males no sperm donation should be allow either during the study or within 120 days after last dose.

6.5.4 USE IN RENAL/HEPATIC DYSFUNCTION/FAILURE

Clinical studies in subjects with renal/hepatic impairment have not been performed to date; therefore, those subjects should be excluded from participation in studies of JNJ-40346527.

6.5.5 OVERDOSAGE AND ABUSE POTENTIAL

Information regarding overdosage and abuse of JNJ-40346527 is not available to date. General

supportive measures should be taken as appropriate.

6.5.6 CONTRAINDICATIONS

There are no contraindications identified at this time for JNJ-40346527.

6.6 **PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES**

No AML-directed concomitant therapy or investigational therapy is allowed during the study. Use of alternative medications (herbal or botanical for anticancer purposes) is not permitted during the study.

7. STUDY PROCEDURES/EVALUATIONS AND SCHEDULE

7.1 STUDY SPECIFIC PROCEDURES

7.1.1 MEDICAL HISTORY

A medical history will be obtained by the investigator or qualified designee. In addition to collecting information on demographics, the medical history will include all active conditions, and any prior conditions that are considered to be clinically significant by the PI. Details regarding the participant's AML will be recorded separately and not listed as medical history.

7.1.2 DISEASE ASSESSMENT

The investigator or qualified designee will obtain prior and current details regarding the participant's AML.

7.1.3 MEDICATION HISTORY

A complete medication history will be acquired concurrent with medical history.

7.1.4 PHYSICAL EXAMINATION

Physical exams must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant or advanced Registered Nurse Practitioner as local law permits. The physical exam at baseline should include a complete physical exam per institutional standards. All other physical exams after baseline will include an evaluation of any AEs, or any previously reported symptoms, or prior physical examination findings.

As part of screening/baseline visit, physical examination is to be conducted within 14 days prior to start of treatment. All physical examinations will also include:

7.1.4.1 *Vital signs*
Vitals to be collected include BP, HR, and temperature. As part of screening/baseline visit, vitals should be obtained within 10 days prior to first dose of study agent. Vitals will also be obtained during treatment.

Significant findings that were present prior to the signature of the informed consent must be included in the Medical History eCRF page. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event eCRF page.

7.1.4.2 *Height and weight*

Height is only required as part of screening.

7.1.4.3 *Performance status*

Performance status will be determined for all participants at screening and at select times during treatment as per assessment schedule in Section 7.10. Refer to Appendix B for performance criteria.

7.1.5 ELECTROCARDIOGRAM (ECG)

A standard of care ECG will be performed within 28 days prior to initiating treatment. Refer to schedule in Section 7.10.

7.1.6 MEDICAL DIARY

Participants that self-administer JNJ-40346527 are required to maintain a medical diary to assess compliance. Participants will receive instruction on how to administer JNJ-40346527 from a physician, clinical research nurse, or other designated, qualified healthcare provider. Participants will be provided with a medical diary and are required to record the date, dose, and the time of each oral dose.

7.1.7 ADVERSE EVENTS

Toxicities and adverse experiences will be assessed at each visit using the CTCAE v5.0. Safety will be monitored by assessing physical examination, vital signs, body weight, performance status, as well as hematology, and chemistry as indicated in Section 7.10.

7.2 **LABORATORY PROCEDURES AND EVALUATIONS**

7.2.1 HEMATOLOGY

Hematologic profiling will be collected per institutional standards, and may include evaluation of hematocrit, hemoglobin, platelets, white blood cells with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and absolute lymphocyte count.

7.2.2 COAGULATION PANEL

INR, prothrombin time, and PTT.

7.2.3 BIOCHEMISTRY

Blood chemistry will be collected per institutional standards and may include the following: Creatinine, BUN, total bilirubin, Alkaline Phosphatase, serum electrolytes, magnesium, calcium, and potassium, phosphorous, as well as lactate dehydrogenase and uric acid. Testing for HCV B or C will only take place during screening

7.2.4 URINALYSIS

Glucose, protein, hemoglobin (blood), bilirubin, ketones, pH, and specific gravity. A microscopic exam should be performed for 2+ (~0.5 to 1.5 g/24 hours) or higher hemoglobin or protein levels.

7.2.5 BONE MARROW EXAM

Bone marrow aspirate must be collected at the visits outlined in the Section 7.10, Schedule of Events (Cycle 1 Day 29, Cycle 2 Day 29, Cycle 3 Day 29, and every 3 months following Cycle 3 Day 29. Additional bone marrow evaluations may occur if clinically indicated at the discretion of

the investigator (e.g., at the time of suspected disease progression or disease remission.)

Bone Marrow Aspirate will be collected to assess:
- Hematopathology review
- myeloid:erythroid ratio per standard of care
- Cellularity (%)
- blast quantification per standard of care.
- Cytogenetics will be performed as standard of care.
- Pharmacokinetic assay described in Section 7.3.1. (5-8ml in sodium heparin)
- Flow cytometry: as standard of care per institutional standards and exploratory analysis described in Section 7.3.2.

7.2.6 SKIN PUNCH BIOPSY

Data analysis from next generation sequencing can be greatly simplified by comparison of a patient's tumor sequence with germline sequence. The comparison facilitates identification of mutations that are unique to the tumor and not inherited sequence polymorphisms. The currently recognized method for obtaining germline sequence (espoused by The Cancer Genome Atlas project) is through the sequencing of DNA from skin fibroblasts that are obtained from a 3.5mm skin punch biopsy. Skin biopsies will be collected during the standard of care bone marrow procedure once during the study. The skin punch biopsy can be collected at any bone marrow collection time point. This procedure replaces the normal skin incision made to access the bone and does not require any additional sterilization or anesthetic.

Briefly, the procedure will be performed with a skin punch. The skin biopsy will be placed in saline or on moist gauze and transported to the research lab. One half of the biopsy will be used for genomic DNA extraction using standard tissue extraction protocols/kits. The remaining half will be snap-frozen and stored at -80ºC.

7.2.7 BLOOD COLLECTION

Blood will be collected at time points outlined in the Section 7.10, Schedule of Events .

Peripheral Blood (2.0 mL in EDTA tube) will be collected for hematologic profiling.

Peripheral Blood (10ml) collected in sodium heparin-coated tubes or sodium citrate tubes will be used for evaluation of serum biochemistry and coagulation, respectively.

Peripheral Blood (10-40 ml) collected in EDTA coated tubes will be used for genetic studies described in Section 7.3.3 and 7.3.4.

7.2.8 PREGNANCY TEST

A serum (β-HCG) or urine pregnancy test is required during screening for all persons of childbearing potential within 14 days of initiating study drug. If the urine pregnancy test is positive, a serum pregnancy test must be performed per institutional standards. Pregnancy tests (serum and/or urine tests) should be repeated, if required, per institutional guidelines.

7.3 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

The two overarching aims of the proposed exploratory studies are to: **(i)** evaluate the pharmacokinetics of JNJ-40346527 and effective inhibition of CSF-1R in marrow aspirates using plasma inhibitory assays with established CSF-1R-sensitive cell lines, and **(ii)** identify the effect of JNJ-40346527 on leukemia cells and the immune microenvironment.

7.3.1 EVALUATE THE PHARMACOKINETICS OF JNJ-40346527 AND EFFECTIVE INHIBITION OF CSF-1R

Plasma inhibitory assays using GDM-1 cells (very sensitive to CSF-1R inhibitors) will be performed with bone marrow aspirates before treatment (no later than 14 days prior to start of treatment) and after 28 days to estimate the effective CSF-1R inhibition by JNJ-40346527 in plasma derived from the marrow. The goal is to evaluate how well JNJ-40346527 inhibits CSF-1R within the marrow microenvironment.

7.3.2 IDENTIFY AND QUANTIFY THE SPECIFIC SUBPOPULATION OF CELLS THAT EXPRESS CSF-1R IN SUBJECTS AND CORRELATE WITH CLINICAL RESPONSE TO JNJ-40346527.

Bone marrow aspirates or peripheral blood will be collected from subjects and analyzed for *ex vivo* sensitivity to JNJ-40346527 prior to entry. The samples will also be analyzed for CSF-1R expression using FACS analysis using the CLIA-certified clinical flow lab at OHSU. In addition to CSF-1R expression, the samples will be analyzed for standard immunophenotypic markers to identify the subpopulation that most highly expresses CSF-1R.

Preliminary data suggests that CSF-1R is expressed on a subset of CD14+ cells (a monocytic marker). This data supports our hypothesis that CSF-1R inhibition is not directly affecting the leukemia cells, but rather is targeting a smaller supportive cell population, as shown in **Figure 4.** Evaluation of pure $CD14^+$ populations in AML samples is somewhat limited since a subset of AML samples express $CD14^+$ on blasts; however, there is still a trend towards sensitivity to CSF-1R inhibition in samples that have higher expression of CSF-1R on non-leukemic CD14+ cells.

CSF-1R expression will be correlated with CD14 and standard immunophenotypic flow markers in the clinical flow lab (Table 5) to determine the specific population(s) that express CSF-1R and are likely to be a target of JNJ-40346527. CSF-1R expression in specific hematopoietic lineages will be correlated with *ex vivo* sensitivity to JNJ-40346527 and clinical response.

The goal of this aim is to identify the specific subpopulation of cells that expresses CSF-1R, and if a quantitative analysis of this population can be used to predict clinical response to CSF-1R inhibition.

Table 5. Clinical flow cytometry antibodies tested with CSF-1R in CLIA-certified lab.

CD1a	CD2	sCD3	cCD3	CD4	CD5	CD7	CD8
CD10	CD11b	CD13	CD14	CD15	CD16	CD19	CD20
CD22	CD33	CD34	CD38	CD45	CD56	CD58	CD64
TdT	CD103	CD23	CD25	CSF-1R			

An identical FACS analysis will also be performed on bone marrow biopsies after one month of therapy to assess the expression of CSF-1R and $CD14^+$ cells after JNJ-40346527 treatment in

both clinical responders and non-responders. This will establish if there is a reduction only in the CSF-1R-expressing population, or if other lineages are also affected. For example, it may be that JNJ-40346527 only affects CD14$^+$ cells that express CSF-1R, or JNJ-40346527 may shrink the entire population of CD14$^+$ cells. The relative proportion of leukemia cells, B-cells, and T-cells will also be evaluated after treatment.

Since this work will be done in a CLIA-certified clinical lab using standard flow procedures and equipment, it would provide a companion diagnostic that could be rapidly incorporated into standard flow protocols for larger trials.

7.3.3 ASSESSING A GENETIC SIGNATURE THAT PREDICTS RESPONSE TO JNJ-40346527.

Genomic DNA from leukemia patients will be analyzed for frequent leukemia mutations to determine if there is a genetic signature that predicts response to JNJ-40346527. The GeneTrails Hematologic Malignancies Gene Panel developed at OHSU's Knight Diagnostic Laboratory covers 76 genes that are frequently mutated in both lymphoid and myeloid leukemia, and is run as a CLIA-approved (CLIA#38D2018256), standard-of-care test on leukemia patients (Refer to D). Additional sites will use their in-house leukemia panel per standard of care. Redacted source documentation from sites will be sent to OHSU for genetic marker analysis.

Sequencing data from participants who have clinically responded to JNJ-40346527 will be compared to that from non-responders, to determine if there are genetic markers of clinical response. The goal is to identify a potential genetic subtype of AML that predicts clinical response to JNJ-40346527, either alone or in combination with the quantitative and qualitative analysis of CSF-1R$^+$ cells.

Additionally, coded and de-identified DNA samples will be stored in the Druker Lab (OHSU) for further retrospective analyses, including targeted sequencing, whole-exome sequencing, or methylation analysis. Samples will be stored indefinitely. Access to samples will be limited to study staff.

7.3.4 TRANSCRIPTOME ANALYSIS TO IDENTIFY POTENTIAL QUALITATIVE DIFFERENCES IN CSF-1R+ CELLS THAT PREDICT PATIENT RESPONSE.

RNAseq will also be performed on leukemia samples from expression signature in CSF-1R$^+$ cells that predicts patient response. We hypothesize that there may be a qualitative difference in CSF-1R$^+$ CD14$^+$ and CSF-1R$^-$ CD14$^+$ cells that results in clinical sensitivity to CSF-1R inhibitors. This difference may not be detected by the CyTOF approach outlined above, as that requires using candidate phospho-protein and cytokines. RNAseq offers an unbiased way to analyze the functional difference between these cells.

CSF-1R$^+$ CD14$^+$ and CSF-1R$^-$ CD14$^+$ cells will be isolated with magnetic antibody sorting. Since not every subject will have sufficient cells for RNAseq, we will review the FACS analysis of patients at screening to identify subjects that are likely to have sufficient numbers of CD14$^+$ and CSF-1R+ cells. Our preliminary data has found that CSF-1R$^+$ cells account for about 1-3% of the total number of cells. 40 ml of peripheral blood will be collected from subjects with a total peripheral blood WBC>10. This WBC typically correlates with a yield of ~100 million cells after Ficoll separation, which will subsequently allow for collection of $\geq$1 million CSF-1R$^+$ CD14$^+$ cells to process for RNA. This peripheral blood sample will be collected on day 1 prior to JNJ-

40346527 treatment.

Collectively, these studies are aimed at identifying a genetic or expression signature of CSF-1R$^+$ cells that predicts clinical response to JNJ-40346527, as well as uncovering potential mechanisms of resistance/adaptation.

7.3.5 MASS CYTOMETRY EVALUATION OF JNJ-40346527 EFFECT ON PHOSPHO-SIGNALING PROTEINS IN IMMUNE CELL POPULATIONS

This exploratory study will utilize mass cytometry (cytometry by Time of Flight, CyTOF) to evaluate the effect that JNJ-40346527 has on intracellular phospho-signaling of proteins within immune cell populations (i.e., cytotoxic T cells, etc.) in pre- and post-treatment samples. These studies are intended to identify biomarkers that predict patient response and prioritize potential combination strategies for future clinical trials.

Bone marrow aspirates and blood samples will be collected and purified by Ficoll gradient. The cells will be fixed and labeled with antibodies coupled to heavy metal isotopes for CyTOF using established protocols. Cells expressing CSF-1R will be evaluated by CyTOF to look at downstream signaling pathways such as phospho-STAT3/5, phospho-Akt, phospho-MAPK, phospho-p38 and phospho-S6. As a positive control, we will use the GDM-1 cell line, which has an activating mutation in CSF-1R and responds robustly to CSF-1R inhibition *in vitro*. Antibodies to identify relevant subpopulations of monocytes, lymphocytes, and leukemia cells will be used to analyze phospho-signaling in CSF-1R$^+$ cells, CD14$^+$ cells, and leukemia cells (**Table 6**).

Table 6. Antibody panel for analysis of kinase signaling and cytokine analysis by CyTOF.

CSF-1R	CD14	pSTAT3	pSTAT5	pMAPK	pS6	pP38	pAkt
EGF	FGF2	HGF	SDF1	VEGF	IL-6	IL-1□	MCP1
MCP2	CXCL1	IL-8	IL-10	RANTES	TGF□	MIP1b	G-CSF
IL3	MIP1a	GCSF-1					

To examine the secreted proteins from the supportive cells, we will pretreat samples with a Golgi trap (brefeldin A) to retain secreted proteins in the cells for intracellular staining. A selection of signaling molecules known to impact leukemia cell survival will also be evaluated, including a focus on the CSF-1R$^+$ and CD14$^+$ cells. Particularly, we will investigate the expression of the ligand CSF-1, which may act in an autocrine manner to expand supportive CSF-1R$^+$ cells ().

Bone marrow aspirates will be tested at screening and after one cycle of therapy to evaluate signaling in CSF-1R$^+$ CD14$^+$ cells, CSF-1R$^-$ CD14$^+$ cells, immune cell populations, and leukemia cells both before and after treatment. Responsive versus non-responsive subjects will be compared to determine if there is a qualitative difference in CSF-1R$^+$ cells that predicts clinical response to JNJ-40346527, and if this population either disappears or is functionally altered by JNJ-40346527 treatment. The goal is to determine if there is a qualitative signature of CSF-1R+ cells that predicts clinical response to JNJ-40346527 that can be used to identify sensitive patients or immunotherapeutic targets in future clinical trials.

In addition to identifying a biomarker, we predict that CSF-1R inhibition will alter the leukemic immune microenvironment as well. This will be evaluated by CyTOF analysis pre- and post-treatment for each patient. Our CyTOF panels cover immune checkpoint proteins, B- and T-cell populations, NK populations, and leukemia surface antigens in addition to the microenvironmental proteins outlined (**Table 6**; **Error! Reference source not found.**). JNJ-40346527 may potentially increase expression of checkpoint proteins, alter specific immune populations such as NK cells, or increase expression of leukemia cell antigens that can be targeted with antibody-directed immunotherapies (CD123, CD33, etc.). **The goal is to identify promising combinations for future immunotherapy clinical trials.**

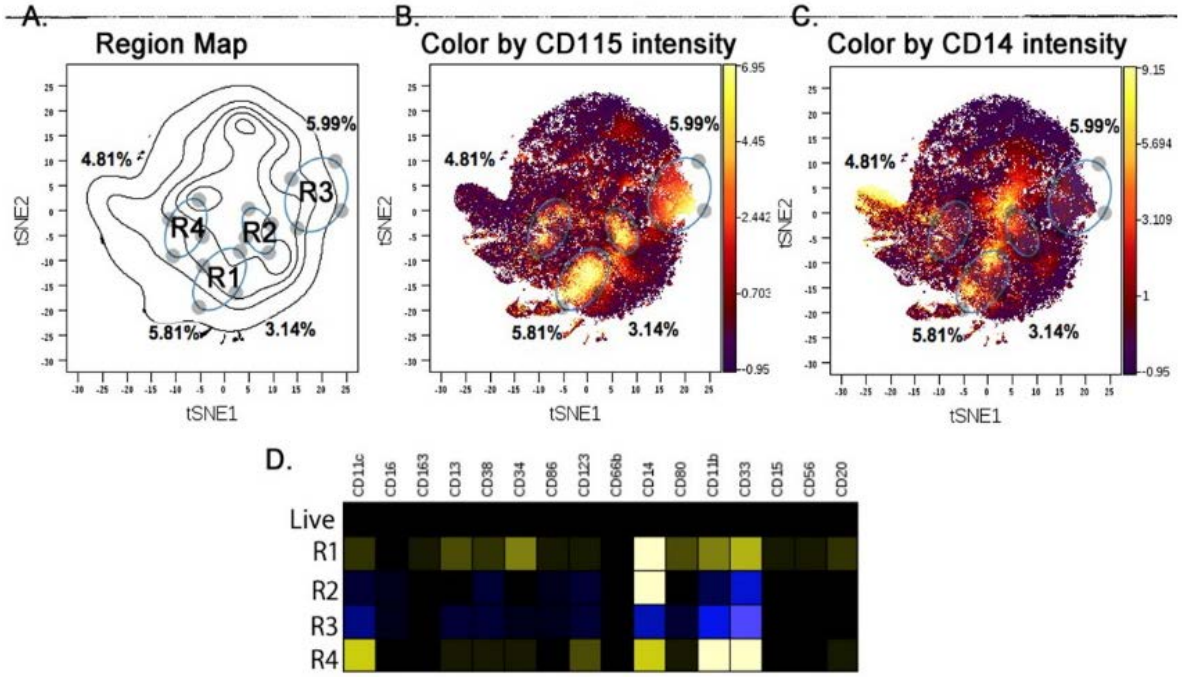

Figure 7. Evaluation of cells expressing CSF-1R and CD14 by CyTOF using viSNE clustering. The AML sample 15-00880 was stained with 35 distinct markers and analyzed by CyTOF. Cell populations expressing CSF-1R (CD115+) were identified, and the gating map is shown in panel **A**. The cell populations that express **B)** CD115 or **C)** CD14 are shown by viSNE cluster analysis displayed as intensity maps for CD115 and CD14, respectively. **D)** The relative fold enrichments of 16 surface markers frequently found in AML show the fold increase compared to all live events for each of the populations defined in panel **A**. We propose to use antibodies that interrogate kinase signaling, immune cell populations, and cytokines (**Table 6**) to obtain functional information about CSF-1R^{+} cell populations in AML.

7.3.6 SCREENING EX VIVO SENSITIVITY TO SMALL MOLECULE INHIBITORS FOLLOWING CSF-1R INHIBITION.

Ex vivo sensitivity to a panel of small molecules will be performed on bone marrow samples pre- and post-treatment to determine how leukemia cells change in response to CSF-1R inhibition. Participants with an *ex vivo* IC_{50} that is ≤20% of the median IC_{50} (to be determined with preclinical testing) will be considered sensitive to JNJ-40346527 (termed “assay positive”), whereas those with an IC_{50} >20% of the median IC_{50} will be considered insensitive (termed “assay negative”).

The *ex vivo* drug screening platform contains ~175 small-molecules inhibitors, including numerous kinase inhibitors. Changes in sensitivity of bone marrow aspirates pre- and post-treatment (day 29) will be evaluated. Preliminary data suggests that CSF-1R inhibition affects secretion of paracrine survival signals from supportive cells in the microenvironment, which will lead to leukemia cell death. Removing paracrine survival signals may also reveal sensitivities to other small molecules that were previously obscured by paracrine survival signals. The goal of these studies is to identify novel drugs that could be used in combination, or sequentially, with JNJ-40346527.

7.4 SCREENING ASSESSMENTS

Toxicities which occur prior to the start of treatment will not be subject to analysis. Consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this research study. Evaluations performed as part of routine care before informed consent can be utilized as screening evaluations if done within the defined time period.

Screening assessments will occur over a 28-day period prior to start of treatment with study agent. Participants will be evaluated for medical history, physical examination, vital signs, ECOG performance status, chest X-ray, concomitant medications, blood sampling for laboratory tests, ECG evaluation, bone marrow biopsy aspiration/biopsy.

E*x vivo* sensitivity analysis of AML cells from either bone marrow aspirate or peripheral blood will be completed no later than 7 days prior to initiating treatment. Peripheral blood may be used in place of bone marrow if participant cannot be aspirated or patient has undergone bone marrow biopsy within the last 10 days prior to desired screening date and blast cells comprise ≥20% of circulating nucleated cells.

7.4.1 INFORMATION TO BE COLLECTED ON SCREENING FAILURES

A participant who signed an informed consent form but failed to be started on treatment for any reason will be considered a screen failure. Those found not to be eligible after signing the main study consent will be considered screening failures, and data will be handled in the same manner. The demographic information and informed consent. No other data will be entered into the clinical database for individuals who are screen failures.

7.5 ASSESSMENTS DURING TREATMENT

Visits will occur on Day 1 of every cycle. Additional visits in cycles 1 and 2 are listed in the schedule of assessments. Under certain circumstances (e.g., clinic holiday, inclement weather) Day 1 may be delayed by not more than 3 days, or occur earlier than scheduled by not more than 3 days during Cycle 2 and subsequent cycles. Specific on-study assessments are listed in the Section 7.10, Schedule of Events .

Initial response to JNJ-40346527 will be assessed by bone marrow biopsy after cycles 1-3 and every 3 months thereafter. Tumor response will be evaluated per International Working Group (IWG) criteria for AML (refer to Section 8). All studies must be obtained ± 7 day of stated time point.

7.6 END OF TREATMENT VISIT

Participants will be followed until death. Participants will be evaluated for end of treatment within ± 7 days after stopping JNJ-40346527. End of treatment assessments are listed in the Section 7.10, Schedule of Events . If participants do not reach the end of treatment due to transition to hospice or death, an end of treatment visit will not be conducted.

7.7 FOLLOW-UP

Participants will be followed every 6 months until death. Participants removed from protocol therapy for unacceptable AE(s) will be followed until resolution or stabilization of the AE.

7.8 EARLY TERMINATION VISIT

Study assessments for an early termination visit will mirror the end of treatment visit. A standard of care treatment plan will be formulated as soon as possible for those participants that withdraw from the study abruptly for any reason. Participants will be encouraged to return for the follow-up visit.

7.9 UNSCHEDULED VISITS

Section 7.10, Schedule of Events lists the mandatory data collected at each time point for the clinical trial but it is expected that additional tests/procedures or visits may occur as standard of care, which is entirely at the discretion of the investigator. Most participants will have additional laboratory studies and clinical evaluations outside of this schedule as part of their standard of care. The labs or studies outlined in the schedule of events may be completed within 7 days of the target week (i.e., 7 days before or 7 days after). Every effort will be made to adhere to this schedule as close as possible. This is the minimum schedule of laboratory studies and follow-up visits required for the study.

7.10 SCHEDULE OF EVENTS

	Screening Period	Treatment Period* (C1D29=C2D1)							End of Treatment†	Follow-up‡
	Cycle	C1	C1	C1	C1	C2	C2	C3+		
	Days -28 to -1	Day +1	Day +8	Day +15	Day +22	Day +1*	Day +15	Day +1		
JNJ-40346527[A]										
Informed consent	X									
Inclusion/exclusion	X									
Medical history	X									
Concomitant Medications[B]	X	X	X	X	X	X	X	X	X	
Physical Exam[C]	X	X	X	X	X	X	X	X	X	
ECG	X									
Chest X-ray[D]	X									
Hematology[E]	X	X	X	X	X	X		X		
Biochemistry	X	X	X	X	X	X		X		
Coagulation Panel	X	X	X	X	X	X		X		
Urinalysis	X					X		X		
Pregnancy test[F]	X	X				X		X		
Bone Marrow[G]	X[H]					X[H]			X	
Flow cytometry	X			X		X				
Cytogenetics	X									
GeneTrails	X									
Skin Punch Biopsy[I]	X[I]									
AE[J]		X	X	X	X	X	X	X	X	X

Ex vivo screening	X		X	X		X				
FACS	X			X		X				
RNAseq	X	X		X		X				
Research Blood Samples[K]	X	X	X	X	X	X		X	X	

***** In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 28 days; however the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 6.2.. If the interval is increased, all procedures except imaging should be performed based on the new dosing schedule.
****** In general, the window for each visit is ± 7 days unless otherwise noted.
******* Point of care CBC will be run every 2 weeks during Cycle 2. Once a cycle in subsequent cycles (Cycle 3+).
† Study treatment will end upon evidence of disease progression as defined by IWG for AML. Refer to Section 8 for additional details.
‡ Participants will be followed until death. Participants may be contacted by phone, and survival status will be collected and documented
[A] JNJ-40346527 (150 mg) is administered PO twice daily.
[B] For concomitant medications – enter new medications started during the trial through the EOT visit. Record all medications taken for grade 3 and 4 SAEs as defined in Section 9.6.
[C] Full physical exam at screening visit. Direct physical exam for all other visits. All physical exams will include assessing weight, vital signs, and ECOG performance status. Height will be measured at screening visit only.
[D] Chest X-ray at screening will be performed within 28 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening image if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment.
[E] After Cycle 1, pre-dose lab samples can be collected up to 72 hours prior to the scheduled time point. Hematology and biochemistry tests should be collected pre-dose on Day 1 of every 28 day cycle. Testing for HCV B or C will only take place during screening.
[F] For women of reproductive potential, a urine pregnancy test should be performed within 14 days prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated, if required, per institutional guidelines.
[G] Peripheral blood may be used in place of bone marrow and blast cells comprise ≥20% of circulating nucleated cells.
[H] Standard of care bone marrow exams are done at screening and Day 29 for Cycles 1-3, and every 3 months for subsequent cycles.
[I] Skin punch biopsy will be collected once anytime during the study.
[J] AEs and laboratory safety measurements will be graded per NCI CTCAE version 5.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. Record grade 3 and 4AEs occurring within 30 days after the last dose of trial treatment. Report grade 3 and 4 hem and non-hem SAEs (related and unrelated to trial treatment) occurring up until 90 days after the last dose of trial treatment, or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs that are related to trial treatment.
[K] Research blood samples will be drawn during standard of care lab draw.

8. EFFICACY MEASURES

8.1 DEFINITION OF EFFICACY MEASURES

Assessment of clinical response will be made according to IWG criteria.[20] The major criteria for judging response will include physical examination and examination of blood and bone marrow. Relevant laboratory studies that are abnormal prior to study will be repeated according to the study schedule to document the degree of maximal response.

8.1.1 EVALUABLE FOR TOXICITY

All participants who have received at least 1 dose of study agent will be evaluable for toxicity from the time of their first treatment with JNJ-40346527.

8.1.2 EVALUABLE FOR OBJECTIVE RESPONSE

Only those participants who have completed at least 1 cycle of study agent will be evaluable.

8.2 RESPONSE CRITERIA FOR AML

The objective response rate will be defined as ≥PR, including cytogenetic and molecular responses when applicable, and will be determined at the end of each cycle.

Complete Remission (CR)*:
- Bone marrow blasts < 5%;
- Absence of blasts with Auer rods;
- Absence of extramedullary disease;
- Absolute neutrophil count >1 x 10^9/L (1000/µL);
- Platelet count > 100 x 10^9/L (100,000/µL);
- Independence of red cell transfusions

Morphologic CR:
- Bone marrow blasts <5%;
- Absence of blasts with Auer rods;
- Absence of extramedullary disease;
- No hematologic recovery required

Partial Remission
- Relevant in the setting of phase 1 and 2 clinical trials only;
- All hematologic criteria of CR;
- Decrease of bone marrow blast percentage to 5% to 25%;
- Decrease of pretreatment bone marrow blast percentage by at least 50%

Cytogenetic Complete Remission (CRc):
- Reversion to a normal karyotype at the time of morphologic CR in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow.

Molecular CR (CRm):
- Molecular studies are negative (i.e., normal molecular markers in persons with previously abnormal molecular studies (e.g. c-KIT, NPM1, FLT3).

CR with incomplete recovery (CRi):	• All CR criteria except for residual neutropenia (< 1 x 10^9/L [1000/µL), or thrombocytopenia (< 100 X 10^9/L [100,000/µL).
Stable disease (SD)	Not fulfilling either PR or PD criteria and clinical stability
Progressive disease (PD)	Increase in blasts by ≥50%

Definitions of response criteria are amended from Cheson et al.[20]

*All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.

8.2.1 OUTCOME MEASURES IN AML

Outcome	Definition	Response Category	Point of Measurement
Overall survival	Defined for all patients of a trial; measured from the date of entry into a study to the date of death from any cause; patients not known to have died at last follow-up are censored on the date they were last known to be alive.	All patients	Trial entry
Event-free survival	Defined for all patients of a trial; measured from the date of entry into a study to the date of relapse from PR or CR or CRi, or death from any cause; patients not known to have any of these events are censored on the date they were last examined.	All patients	Trial entry

9. SAFETY

9.1 SPECIFICATION OF SAFETY PARAMETERS

As the sponsor of the Study, INSTITUTION and PRINCIPAL INVESTIGATOR shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations

The Investigator is responsible for monitoring the safety of participants who have enrolled in the study. Safety assessments will be based on medical review of adverse events and the results of safety evaluations at specified time points as described in Section 7.10, Schedule of Events. Any clinically significant adverse events persisting at the end of treatment visit will be followed by the Investigator until resolution/stabilization or death, whichever comes first.

Management of Safety Data
This Study has been designated as an interventional study. As such, all adverse events for Janssen Medicinal Products regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this section will be reported from the time a subject has started study drug until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

For the purposes of this study, the Janssen medicinal product is: JNJ-40346527

9.2 DEFINITIONS

9.2.1 ADVERSE EVENT (AE)

An adverse event is defined as any undesirable physical, psychological or behavioral effect experienced by a participant during their participation in an investigational study, in conjunction with the use of the investigational product, whether or not considered intervention-related (21 CFR 312.32 (a)). In general, this includes signs or symptoms experienced by the participant from the time subject has started study drug to completion of the study.

AEs may include, but are not limited to:
- Subjective or objective symptoms spontaneously offered by the participant and/or observed by the Investigator or medical staff.
- Clinically significant laboratory abnormalities.
- A significant worsening of the participant's condition from study entry.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment that resolve but then recur after treatment.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment which increase in frequency, intensity, or a change in quality after treatment.

9.2.2 SERIOUS ADVERSE EVENT (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- In-patient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and/or participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include:

- Allergic bronchospasm requiring intensive treatment in an emergency room or at home,
- Blood dyscrasias or convulsions that do not result in in-patient hospitalization, or
- The development of drug dependency or drug abuse.

Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience, the investigator may choose to hospitalize the subject for the duration of the treatment period.

Life-Threatening Conditions

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition

9.2.3 UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers UPs involving risks to participants or others to include, in general, any incident, experience, or outcome that meets <u>all</u> of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

This study will use the OHRP definition of UP.

9.2.4 SEVERITY OF EVENT

The Investigator will grade the severity of each AE using, when applicable, the current version of the CTCAE v5.0. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as defined below:

- **Mild** (grade 1) – An event that is usually transient in nature and generally not interfering with normal activities
- **Moderate** (grade 2) – An event that is sufficiently discomforting to interfere with normal activities
- **Severe** (grade 3) – An event that is incapacitating with inability to work or do usual activity, or inability to work or perform normal daily activity
- **Life-threatening/debilitating** (grade 4) – An event that puts the participant at immediate or potential risk of death, requires hospitalization, or which drastically impacts a participant's well-being
- **Fatal** (grade 5)

9.2.5 ASSESSMENT OF CAUSALITY RELATIONSHIP TO STUDY AGENT

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- *Definite* – The AE is clearly related to the study treatment.
- *Probable* – The AE is likely related to the study treatment.
- *Possible* – The AE may be related to the study treatment.
- *Unlikely* – The AE is doubtfully related to the study treatment.
- *Unrelated* –The AE is clearly NOT related to the study treatment.

9.3 **EXPECTEDNESS**

Dr. Elie Traer will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent. The coordinating center will submit reports to Janssen as outlined in the section 9.6.2.

9.4 **ADVERSE EVENT LIST(S)**

9.4.1 ADVERSE EVENT LIST FOR JNJ-40346527

Detailed information about the risks and expected AEs of JNJ-40346527 may be found in the current edition of the manufacturer's IB. [a] The most frequently reported AEs (occurring in ≥20% of participants) by preferred term were pyrexia (11 [52.4%]), nausea (7 [33.3%]), headache (7 [33.3%]), vomiting (6 [28.6%]), and anemia (5 [23.8%]). Severe (CTCAE Grade 3) AEs were reported in 7 (33%) participants and included anemia, lymphopenia, gastric obstruction, peripheral edema, abnormal hepatic function, increased lipase, and hypoalbuminemia. A single subject experienced a CTCAE Grade 4 dyspnea.

9.5 **ADVERSE EVENT ASSESSMENT AND FOLLOW-UP**

The occurrence of an UP, AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product. Information to be collected includes event description, time of onset, clinician's assessment of severity, seriousness, expectedness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The Investigator will record all reportable events with start dates occurring any time after the subject has started study drug until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug or until the participant receives alternative therapy for his/her AML, whichever occurs first. Any SAE that occurs after treatment with alternative therapy will be reported only if the Investigator or current treating physician has assessed the SAE as related to the study treatment. Adverse events will be evaluated using the current version of the CTCAE v5.0.

An adverse event as described in this section will be reported from the time a subject has started study drug until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

9.6 REPORTING PROCEDURES

9.6.1 OHSU IRB REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Unanticipated Problems and AEs will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site.

Events that must be reported by the Investigator to the IRB are detailed in the OHSU IRB **Investigator Guidance: Prompt Reporting Requirements (HRP-801)**. At a minimum, events requiring reporting to the IRB include:

- Any new or increased risk related to the research, including AEs or IND safety reports that require a change to the protocol or consent,
- Publications identifying new risks,
- Data Safety Monitoring Board/Committee letters recommending changes or discussing new risks
- Unanticipated adverse device effect
- Unauthorized disclosure of confidential participant information

9.6.2 CENTRAL REPORTING OF ADVERSE EVENTS FOR MULTICENTER STUDIES

A participating site must report an SAE to the institution's local IRB for action as required, as well as to the OHSU coordinating center study team by phone, fax, or email within 24 hours of learning of the event. The participating center will send the coordinating center materials regarding the SAE, as well as any other study-related documentation requested by the OHSU study team.

The OHSU coordinating center study team will review and submit SAEs to the FDA, OHSU IRB, and any other required contacts as required by the Knight Data Safety Monitoring Plan (DSMP). The PI at the Coordinating Center is responsible for distributing IND and/or IDE Action Letters or Safety Reports, as applicable, to participating institutions for review and submission to their institution's local IRB.

9.6.3 SAE REPORTING

The Sponsor is required to report SAEs with the provided Janssen SAE form. Adverse events to be reported include any UPs (i.e., not listed in the package insert) and any SAEs with a suspected association to the investigational product.

9.6.4 SPONSOR OR ADDITIONAL REPORTING REQUIREMENTS

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible, but in no event later than 7 calendar days after initial receipt of the information. All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible, but in no event later than 15 calendar days after initial receipt of the information. All events reported to the FDA will also be reported to Janssen Research and Development, LLC as provided in the Research Agreement within 24 hours the investigator becomes aware of the SAE. This information should

be transmitted to Janssen via the Janssen Serious Adverse Event Report Form via secure email to IIS-BIO-VIRO-GCO@its.jnj.com.

Special Reporting Situations

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product

These safety events may not meet the definition of an adverse event; however, from a COMPANY perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to the COMPANY **within 24 hours of becoming aware of the event.**

Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Suspected Contamination
- Suspected Counterfeit

PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and the COMPANY, and are mandated by regulatory agencies worldwide. The COMPANY has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to the COMPANY by the PRINCIPAL INVESTIGATOR **within 24 hours after being made aware of the event.** The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PRINCIPAL INVESTIGATOR must report the PQC to the COMPANY according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the COMPANY.

9.6.5 REPORTING OF PREGNANCY

All initial reports of pregnancy must be reported to the COMPANY by the PRINCIPAL INVESTIGATOR **within 24 hours of becoming aware of the event** using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

No fertility studies have been performed to date. However, JNJ-40346527 may elicit embryofetal toxicity. JNJ-40346527 can only be administered in female and male subjects who practice effective birth control methods. Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the PRINCIPAL INVESTIGATOR **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

9.7 STUDY STOPPING RULES

The overall study will be paused, and appropriate authorities (e.g., IRB, Knight Data and Safety Monitoring Committee) notified if the following events occur:

- Life-threatening grade 4 toxicity attributable to protocol therapy that is unmanageable, or unexpected [detail specific events as appropriate].
- Death suspected to be related to JNJ-40346527.
- As indicated by statistical stopping rules in Section 10.2.4.

10. STATISTICAL CONSIDERATIONS

Refer to Section 3.1, Description of the Study Design for a detailed description of the study design and endpoints.

10.1 ANALYSIS POPULATIONS

Most common analysis populations are described below:

Analysis Population	Definition	Endpoint
Intent to Treat (ITT)	Those who consent and are registered for the trial regardless of actual receipt of screening or treatment	Used to report accrual
Evaluable for Safety	Those who received at least one dose of JNJ 40346527	Incidence of DLT and SAE
Evaluable for Response	Those who received at least one cycle of JNJ 40346527 and have response measurements	Best objective response
Evaluable for Overall Survival and Event-Free Survival	Those who received at least one dose of JNJ 40346527 and have survival information	Overall survival

10.2 DESCRIPTION OF STATISTICAL METHODS

10.2.1 ANALYSIS OF PRIMARY ENDPOINT(S)

A Simon 2-stage minimax design will be used to determine best objective response. For each arm, we will enroll 7 patients in the first stage. If there is at least 1 response among the first 7 patients, we will proceed to the second stage and enroll an additional 7 patients. The treatment is considered promising if we have at least 3 responses among 14 patients. We will estimate the best objective response and exact confidence interval using the binomial distribution for each arm separately.

Response assessment will be based on best objective response rates within the first 2 cycles of study drug, including CR, CR with inadequate bone marrow recovery, partial response, stable disease, or progressive disease as defined by Cheson et al.[20]

10.2.2 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For the secondary endpoints, we will estimate the incidence of the overall incidence of treatment-related and non-treatment related toxicityand the exact confidence interval. In addition, each toxicity event will be tabulated and summarized by severity and major organ site according to the CTCAE v5.0. Time-to-event analysis (e.g., Kaplan-Meier and cumulative incidence curves) will be used to evaluate event-free and overall survival.

10.2.3 ANALYSIS OF THE EXPLORATORY ENDPOINT(S)

10.2.3.1 *Transcriptome analysis to identify potential qualitative differences in CSF-1R$^+$ cells that predict patient response*

For statistical analysis, we will need >5 responders and non-responders. We anticipate this will be feasible with 14 participants enrolling on the assay positive arm (not all will respond in vivo, and the non-responders can be used for comparison). In addition, we will also collect samples from the 7 patients enrolling on the assay negative arm who are likely to be non-responders.

If sufficient participants initially respond to JNJ-40346527 but later develop resistance, we will also collect these resistant samples to be analyzed by RNAseq as a separate comparison group. This may provide insight into how patients develop resistance to JNJ-40346527.

10.2.4 INTERIM ANALYSIS AND STOPPING RULES

This study will consist of 2 stopping rules: one for futility (lack of efficacy) and another for excess toxicity.

For futility, we will follow the stopping rule based on the Simon's 2-stage design with the minimax criteria. Specifically, if there is no response among the first 7 patients after receiving 2 cycles of study agent, the arm will not proceed to the second stage.

For excess toxicity, we will suspend enrollment if the lower 90% confidence interval for Grade 3 or higher treatment-related toxicity exceeds 30% (considered acceptable dose-limiting toxicity (DLT) incidence). We will then conduct a comprehensive toxicity evaluation and consult with the Knight Cancer Institute's Data and Safety Monitoring Committee for guidance on possible modifications of the protocol, including termination of one or more of the arms, dose modification, and/or changes in eligibility criteria

10.2.4.1 *Safety Stopping Rule*

Temporarily suspend the trial if the number of patients with DLT is equal to or greater than the number shown below:

N	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
DLT	3	4	4	5	5	5	6	6	7	7	7	8	8	9	9	9	10

The safety boundary is also show in **Figure 4. Toxicity stopping rule.**Figure 4.

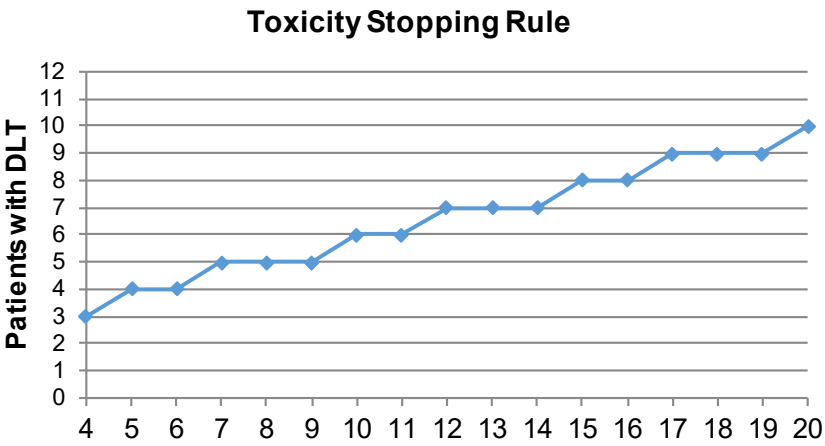

Figure 4. Toxicity stopping rule. If the number of patients with DLT is on the boundary or exceeds the boundary, suspend the trial due to safety.

10.3 SAMPLE SIZE, POWER, ACCRUAL RATE AND STUDY DURATION

10.3.1 SAMPLE SIZE AND POWER

The sample size for each group was derived according to the 2-stage design with minimax criteria using the following parameter settings: 1) 80% power; 2) 5% significance level; 3) historical response rate of 5% (poor response), and 4) desired response rate of 30% (promising response).[21] The sample size and power analyses were conducted using PASS 14 software (http://www.ncss.com/software/pass/). Based on the expected accrual rate of 14 participants per year, we anticipate this trial to take 36 months (24 months of accrual and 12 month of minimum follow-up).

10.4 HANDLING OF MISSING DATA

Missing data will not be imputed. Whenever possible, the analysis will be conducted using all available data. Missing data will be reported in the descriptive summary, and it will be noted if some subjects are excluded from the analysis due to missing data.

11. CLINICAL MONITORING

11.1 OHSU KNIGHT CANCER INSTITUTE DATA & SAFETY MONITORING PLAN

This study is under the oversight of the Knight Cancer Institute's DSMC as described in the Knight institutional DSMP. The Knight DSMP outlines the elements required to ensure the safety of clinical trial participants, the accuracy and integrity of the data and the appropriate modification of cancer-related clinical trials for which significant benefits or risks have been discovered or when the clinical trial cannot be successfully concluded. The Knight DSMP also describes the methods and procedures for ensuring adequate oversight of cancer-related research at OHSU.

As described in the Knight DSMP, regardless of a trial's risk level and any specific Knight oversight in place, the Investigator is singularly responsible for overseeing every aspect of the design, conduct, and final analysis of his/her investigation.

The Knight DSMC will review and monitor study progress, toxicity, safety and other data from this study. Information that raises any questions about participant safety or protocol performance will be addressed by the Investigator, statistician and study team. Should any major concerns arise, the Knight DSMC may recommend corrective action and determine whether or not to suspend the study.

The Knight DSMC will review each protocol every 6 months, but may occur more often, if required, to review toxicity and accrual data (please refer to Knight DSMP for additional details on audit frequency). The Knight DSMC will review accrual, toxicity, response and reporting information. Information to be provided to the DSMC may include: participant accrual; treatment regimen information; AEs and SAEs reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. laboratory values) will be provided upon request.

11.2 CLINICAL DATA & SAFETY MONITORING

Monitoring visits will be performed during the study to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, and that the conduct of the trial is in compliance with the protocol, GCP, and applicable regulatory requirements.

Details of monitoring activities, including designation of assigned monitoring entities, scope of monitoring visits, timing, frequency, duration of visits, and visit reporting, will be included in a separate TSMP that is reviewed and approved by the Knight DSMC and IRB according to the DSMP v5.1.

The Investigator agrees that the monitor will be permitted to conduct monitoring visits at appropriate intervals. The Investigator agrees to provide all relevant information and documentation as requested by the monitor, including access to all original study documents and source data, including access to electronic medical records and/or source documents if necessary.

The monitor will conduct source data review and verification as outlined in the TSMP, and following each visit will generate a report summarizing the visit findings.

Regardless of monitoring entity, the Sponsor is ultimately, singularly responsible for overseeing every aspect of the design, conduct, and final analysis of the investigation.

If at any time Investigator noncompliance is discovered at OHSU, the Sponsor shall promptly either secure compliance or end the Investigator's participation in the study.

Independent audits may be conducted by the Knight DSMC to verify that the rights and well-being of human participants are protected, that the reported trial data are accurate, that the conduct of the trial is in compliance with the protocol and applicable regulatory requirements, that monitoring practices are adequate and in compliance with the monitoring plan, and that evidence of ongoing investigator oversight is present.

11.3 **QUALITY ASSURANCE & QUALITY CONTROL**

The investigational site will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring by the monitor and/or sponsor, and auditing by the Knight DSMC and/or regulatory authorities.

Quality assurance (QA) auditing activities will occur as detailed in the Knight DSMP. All discrepancies, queries, deviations, observations, and findings will be compiled into a final audit report along with a Corrective and Preventative Action Plan.

The Sponsor-investigator, or study monitor, will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

12. DATA HANDLING AND MANAGEMENT RESPONSIBILITIES

12.1 SOURCE DATA/DOCUMENTS

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The Investigator will maintain adequate case histories of study participants, including accurate CRFs, and source documentation.

12.2 PARTICIPANT & DATA CONFIDENTIALITY

The information obtained during the conduct of this clinical study is confidential, and unless otherwise noted, disclosure to third parties is prohibited. Information contained within this study will be maintained in accordance with applicable laws protecting participant privacy, including the provisions of the Health Insurance Portability and Accountability Act (HIPAA).

Participant confidentiality is strictly held in trust by the participating Investigator(s) and study team. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or manufacturer supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Upon enrollment, participants will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files for data analysis will contain only the participant code. Codes will not contain any part of the 18 HIPAA identifiers (e.g., initials, DOB, MRN). The key associating the codes and the participants' personally identifying information will be restricted to the Investigator and study staff. The key will be kept secure on a restricted OHSU network drive - in a limited access folder.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored within the Knight Cancer Institute per OHSU's Information Security Directives. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Knight Cancer Institute research staff will be secured and password protected per OHSU's Information Security Directives. At the end of the study, all study databases will be de-identified and archived within the Knight Cancer Institute.

12.3 DATA COLLECTION & STORAGE: PRIVACY, CONFIDENTIALITY & SECURITY

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Standard institutional practices will be followed as described in the OHSU's Information Security Directives to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures.

Loss of participant confidentiality is a risk of participation. Efforts will be made to keep study participant identities confidential except as required by law. Participants' samples will be identified by code only and stored in OHSU protocol #4422. Specifically, each consenting participant will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will also be used to identify any participant specific samples.

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical information research system (eCRIS), hosted on OHSU secure servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Any additional printed documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

Study outcome data will be captured in electronic case report forms (eCRFs) using an electronic data capture (EDC) system, REDCap Cloud. The REDCap Cloud EDC is a web-hosted application hosted by nPhase (located in Encinitas, CA), and is an approved EDC system that has been reviewed by OHSU Security. To further preserve confidentiality, PHI in the EDC system will be limited to just demographics, birth date and visit dates. The web-accessible EDC system is password protected and encrypted with role-based security, and administered by designated informatics staff within OHSU or Knight Cancer Institute. All users of the database are assigned a unique ID, username, and password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database.

Data from correlative studies will be entered into the RedCap Cloud EDC system by study personnel at OHSU. All other electronic data extracts will be stored only on OHSU computers and restricted drives, limited only to study investigators and staff with authorization to access the data. Quality assurance will be conducted as outlined in Section 11.3, Quality Assurance & Quality Control.

12.3.1 FUTURE USE OF STORED SPECIMENS

Each participant who signs consent will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will be used to identify any participant specific samples. Blood and bone marrow samples collected for the purposes of this protocol will be stored under OHSU protocol #4422 until they can be analyzed in the Druker Laboratory.

12.4 **MAINTENANCE OF RECORDS**

Records and documents pertaining to the conduct of this study, source documents, consent forms, laboratory test results and medication inventory records, must be retained by the

Investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indicate, until 2 years after the investigation is discontinued and FDA is notified. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the sponsor to inform the Investigator when these documents no longer need to be retained.

If the Investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution or another investigator at OHSU. Records must be maintained according to institutional or FDA requirements.

12.5 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will adhere to the requirements set forth by the ICMJE and FDAAA that requires all clinical trials to be registered in a public trials registry (e.g., ClinicalTrials.gov) prior to participant enrollment.

12.6 DELIVERY OF PROGRESS REPORTS TO STUDY FUNDER

Upon the request of Janssen Research & Development, LLC, the Institution will submit oral or written reports on the progress of the Study as provided by this protocol. Within one hundred twenty (120) days following the completion or termination of the study, Institution will furnish Janssen Research & Development, LLC with a final report detailing the results of this study.

13. ETHICS/PROTECTION OF HUMAN PARTICIPANTS

13.1 ETHICAL STANDARD

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR 312 (for IND studies), 21 CFR 812 (for IDE studies), and/or the ICH E6.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT

Written informed consent will be obtained from all participants, or the legally authorized representative of the participant, participating in this trial, as stated in the Informed Consent section of 21 CFR Part 50. If a participant's signature cannot be obtained, and for all participants under the age of 18, the Investigator must ensure that the informed consent is signed by the participant's legally authorized representative. Documentation of the consent process and a copy of the signed consent shall be maintained in the participant's medical record.

13.3.1 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families as appropriate. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks/benefits of the study, alternatives to participation, and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 PROTOCOL REVIEW

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute's Clinical Research Review Committee (CRRC) and the appropriate IRB prior to any participant being consented on this study.

13.5 **CHANGES TO PROTOCOL**

Any modification of this protocol must be documented in the form of a protocol revision or amendment submitted by the Investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the participant. In that event, the Investigator must notify the IRB and Sponsor within 5 business days after the implementation.

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15. APPENDICES

APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: SUMMARY OF CAUTIONARY MEDICATIONS

Summary of Cautionary Medications

Category	Drug Name
Strong CYP3A4/5 inhibitors	Voriconazole, Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
Strong CYP3A4/5 inducers	Avasimibe[2,3], carbamazepine, mitotane, nafcillin, nevirapine, oxcarbazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampin (rifampicin)[3], St. John's wort (hypericum perforatum)[3]
CYP3A4/5 substrates with NTI[1]	Terfenadine, Alfentanil, apixaban (doses >2.5 mg only), aprepitant, astemizole, cisapride, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, lovastatin, nicardipine, nisoldipine, pimozide, quinidine, rivaroxaban, simvastatin, sirolimus, tacrolimus, terfenadine, thioridazine
Pgp inducers	Aliskiren, colchicine, dabigatran, digoxin, everolimus, fexofenadine, loperamide, marovirac, posaconazole, ranolazine, saxigliptan, sirolimus, sitagliptin, and tolvaptan

[1] NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).
[2] Herbal product
[3] P-gp inducer

APPENDIX C: CONTRACEPTION

For men and women contraception should be in place during study and for a minimum of 120 days since the last dose of study drug for both men and women,

For Males Subjects Participating in the Study:
The following methods have been determined to be more than 99% effective (failure rate less than 1% per year, when used consistently and correctly) (Trussell, 2004), by the male subject and his partner and are permitted under this protocol:

- Complete abstinence from sexual intercourse
- Double barrier methods
  - Condom with spermicide in conjunction with use of an intrauterine device (IUD)
  - Condom with spermicide in conjunction with use of a diaphragm
- Oral, injectable, or implanted contraceptives
- Tubal ligation or vasectomy (surgical sterilization)
- Avoid sperm donation within the treatment period and 120 days after the last study drug dose

For Female Subjects Participating in the Study:
The following methods have been determined to be more than 99% effective (failure rate less than 1% per year, when used consistently and correctly) (Trussell, 2004), by the female subject and her partner and are permitted under this protocol:

- Complete abstinence from sexual intercourse
- Double barrier methods
  - Condom with spermicide in conjunction with use of an IUD
  - Condom with spermicide in conjunction with use of a diaphragm
- Tubal ligation or vasectomy (surgical sterilization)
- Oral, injectable, or implanted contraceptives

Subjects >55 y/o and without menses for at least 3 years are considered in menopause.

APPENDIX D: HEMATOLOGICAL MALIGNANCY GENE PANEL

Gene Categories

Kinase
ABL1,
ATM,
BRAF,
CCND1,
CDKN2A,
JAK1,
JAK2,
JAK3,
STAT3

Receptor Tyrosine Kinase
FLT3
KIT

Receptor
CSF3R
GNA13
IL7R
MPL
NOTCH1
NOTCH2

Transcription
BCOR
BCL6
CEBPA
CREBBP
ETV6
EP300
FOXO1
GATA1
GATA2
MEF2B
MLL
MLL2
MYC
1D3
IKZF1
PAX5
PHF6
PRDM1
RUNX1
STAT3
TDF3
WT1

Epigenetic
ASXL1
DNMT3A
EZH2 KDM6A/UTX
PTEN
SUZ12
TET

Phosphatase
PTPN11

Splicing
SF3B1
SRSF2
U2AF35
ZRSR2

RAS
HRAS
KRAS
NRAS

Adaptor
CBL
CBL-B
MYD88

Ubiquitin
BIRC3
FBXW7
TNFAIP3
TNFRSF14

Cohesin-Complex gene
RAD21
SMC1A
SMC3
STAG2
Other
CALR
CARD11
CD79A
BCL2
FAM5C
HNRNPK
IDH1
IDH2
NPM1