AML 48

A Phase II Study Assessing CPX-351 (Vyxeos™) with Quizartinib for the Treatment of Relapsed or Refractory FLT3-ITD Mutation-Positive AML

DEVELOPMENT INNOVATIONS STUDY NUMBER:	AML 48
STUDY DRUG:	Quizartinib
SPONSOR:	Sarah Cannon Development Innovations, LLC 1100 Dr. Martin L. King Jr. Blvd Suite 800 Nashville, TN 37203 844-710-6157 CANN.SCRIInnovationsEnr@scri-innovations.com
STUDY CHAIR:	Michael Tees, MD, MPH Oncologist Colorado Blood Cancer Institute 1721 E. 19th Avenue Suite 300 Denver, CO 80218 720-754-4800 Office
DATE FINAL:	11 March 2019

AMENDMENT NUMBER:	**1**	**AMENDMENT DATE:**	**08 October 2019**
AMENDMENT NUMBER:	**2**	**AMENDMENT DATE:**	**20 November 2019**
AMENDMENT NUMBER:	**3**	**AMENDMENT DATE:**	**10 August 2020**

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Clinical Study Statement of Compliance

AML 48

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

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

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

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Clinical Study Protocol Approval Page

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Michael Tees, MD, MPH

Study Chair
Oncologist
Colorado Blood Cancer Institute
1721 E. 19th Avenue
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Study Chair Signature

Date

Marcy Vallone

Sarah Cannon Development Innovations, LLC
President
Sarah Cannon Development Innovations

Sarah Cannon Development Innovations, LLC Representative Signature

Date

SARAH CANNON
Fighting Cancer Together™

Clinical Study Principal Investigator Signature Form

A Phase II Study Assessing CPX-351 (Vyxeos™) with Quizartinib for the Treatment of Relapsed or Refractory FLT3-ITD Mutation-Positive AML

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

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

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

Sarah Cannon Development Innovations, LLC
1100 Dr. Martin L. King Jr. Blvd., Suite 800
Attention: AML 48 Study Team
Nashville, TN 37203

AML 48 CONTACT INFORMATION

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Development Innovations Enrollment Email:	CANN.SCRIInnovationsEnr@scri-innovations.com

AML 48 AMENDMENT SUMMARY OF CHANGES

AMENDMENT NUMBER: 3 **AMENDMENT DATE:** 10 August 2020

Additions are noted by **bolding**. Deletions are noted by ~~cross outs~~. Only the parts of sections with changes are presented. Please note that formatting changes and minor changes to punctuation, spelling, and abbreviations that do not affect meaning are not noted in this summary.

Global Changes

- Throughout the document "Sarah Cannon Development Innovations" is now abbreviated as "~~Sarah Cannon~~ **Development** Innovations"
- Sarah Cannon Development innovations address has been updated to 1100 Dr. Martin L~~uther~~ King Jr. Blvd
- Throughout the study the time hematologic toxicities have for count recovery **56** ~~42~~ days

Protocol Synopsis-Study Drug and Mode of Administration:

- The following statements have been added:
    - **Any patient with neutropenia or thrombocytopenia lasting ≥56 days from the initiation of CPX-351 will not receive consolidation and will instead proceed to the maintenance phase.**
    - The maintenance phase is a 28-day cycle beginning 7 days (± 7) after neutrophil recovery **(ANC >1000/µL)** from the consolidation phase or induction phase

Protocol Synopsis-Inclusion Criteria:

- Several erroneous "~~?~~" symbols were removed and replaced with "≤"

Protocol-Synopsis Exclusion Criteria:

- The following statement has been revised to include contraception exclusion criteria "Female patients who are lactating or have a positive serum pregnancy test during the screening period. **Female patients of childbearing potential who are not willing to employ highly effective birth control (as defined in Appendix C) from screening to 6 months following the last dose of CPX-351 and/or quizartinib."**
- The following statement has been added to include male reproductive exclusion criteria **Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential must use condoms plus a spermicidal agent during the study treatment period and for 6 months following their last dose of CPX-351 and/or quizartinib, and must not father a child during this period. (Refer to Appendix C)**
- **"**QTcF interval using Fridericia's correction factor (QTcF) interval prolongation, defined as >450 msec at screening and ~~day 8~~ prior to first administration of quizartinib."
- The following sentence has been added "**Any patients with known significant impairment in gastrointestinal (GI) function or GI disease that may significantly alter the absorption of quizartinib**." The following redundant statement has been removed "~~Any patients with known significant impairment in gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of quizartinib.~~"

- "**Patients with inadequate** ~~adequate~~ pulmonary function **will be excluded**. **Inadequate pulmonary function is defined as requiring** ~~(no~~ supplemental O_2**,** or diffusing capacity of the lungs for carbon monoxide [DLCO] <40%~~)~~"

Section 1.5 Risks and Benefits

- ~~In early phase studies, quizartinib has been associated with Grade 2 or higher QTc Fridericia's correction factor (QTcF) prolongation (11%) (Hills et al 2015).~~ **Quizartinib has been associate with QT prolongation in a dose dependent manner. In study AC220-007 (Quantum-R) in the relapse/refractory FLT3+ AML population, Eight (3.3%) subjects in the quizartinib arm had ECG QTcF values >500 ms (Grade 3 QTcF) by central ECG reading. (Quizartinib Investigator Brochure 2020**

Section 2.3.1 Primary Endpoints

- "Complete remission (CR) defined as a complete morphologic response with complete blood count recovery ANC ~~>~~ ≥1000/µL and~~/or~~ platelet count ~~>~~ ≥100,000/µL),

Section 3.2 Exclusion Criteria

- The following statement has been revised to include contraception exclusion criteria "Female patients who are lactating or have a positive serum pregnancy test during the screening period. **Female patients of childbearing potential who are not willing to employ highly effective birth control (as defined in Appendix C) from screening to 6 months following the last dose of CPX-351 and/or quizartinib."**

- The following statement has been added to include male reproductive exclusion criteria **Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential must use condoms plus a spermicidal agent during the study treatment period and for 6 months following their last dose of CPX-351 and/or quizartinib, and must not father a child during this period. (Refer to Appendix C)**

- "QTcF interval using Fridericia's correction factor (QTcF) interval prolongation, defined as >450 msec at screening and ~~day 8~~ prior to first administration of quizartinib."

- "**Patients with inadequate** ~~adequate~~ pulmonary function **will be excluded**. **Inadequate pulmonary function is defined as requiring** ~~(no~~ supplemental O_2**,** or diffusing capacity of the lungs for carbon monoxide [DLCO] <40%~~)~~"

Section 3.3 Discontinuation from Study Treatment

- Pregnancy **and breastfeeding**

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

  ~~All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the Investigator, not likely that these values will improve. In this case, the~~

~~Investigator must record his or her reasoning for making this decision in the patients' medical records.~~

Section 5 Study Design

- A total of 10 patients will be enrolled in the safety lead-in. The safety lead-in portion of the study is designated as Part 1. ~~If the first 10 patients meet the pre-specified safety parameters, an additional 24 patients will be enrolled in Part 2 of the study~~ **If >3 patients experience delayed neutrophil count recovery >56 days from the first day on the study regimen, or delayed thrombocytopenia recovery >56 days from the first day on the study regimen, or if >3 patients develop a non-hematologic toxicity, defined as a Grade 4 non-hematologic adverse event determined to be probably related to the combined treatment, or a Grade 4 neutropenia, then the study will be terminated. Assuming safety parameters are met, the first 10 patients will be followed for response in the Part 2 of the study.** ~~If the first 10 patients meet the pre-specified safety parameters,~~ An additional 24 patients will be enrolled in Part 2 of the study (induction, consolidation, and maintenance). All patients will be assessed for response.
- Patients who experience an AE that results in the discontinuation of study treatment will be followed until **resolution/stabilization for AEs attributed to the medication.** ~~resolution of the AE.~~ Outcomes for all patients will be assessed for 24 months from the ~~start of study treatment~~ **date of last treatment.**
- The study schema and study schema footnotes have been updated for clarity.

Section 5.2.4 Maintenance Phase

- The maintenance phase consists of 28-day cycles. Patients will receive quizartinib once daily for a total of 24 cycles or until disease relapse. Maintenance dosing of quizartinib will begin at 30 mg PO once daily on Days 1-14, and if there are no non-hematologic Grade ≥3 toxicities and QTcF is maintained ≤450 msec, the quizartinib dose will increase to 60 mg/day on Day 15. If consolidation therapy is not advised **at all or if only 1 cycle of consolidation is advised** based on prolonged toxicities, maintenance therapy will begin 7 days (±7) after neutrophil recovery **(ANC >1000/µL)** from the consolidation phase or induction phase. ~~Patients will receive quizartinib once daily for a total of 24 cycles or until disease relapse.~~
- Patients who proceed to alloHCT or other CT intervention after consolidation will resume quizartinib maintenance no earlier than Day 30 from the intervention **or transplant.** ~~For a total of 24 cycles or until disease relapse.~~ ~~In patients who proceed to alloHCT, initiation of quizartinib maintenance should begin no earlier than Day 30 after transplant.~~ If ≥2 CT interventions (e.g., repeat DLI) are planned after maintenance, a 28-day hold is acceptable, with resumption of quizartinib with the next cycle. **If the patient is on quizartinib prior to HCT or CT intervention, quizartinib should be discontinued 7 days prior if a conditioning therapy is utilized. If proceeding to a CT intervention without conditioning therapy (e.g., DLI), quizartinib should be discontinued one day prior to CT intervention.**

Section 5.3.2 Prohibited Concomitant Medications

- Links to **Appendix F** and **Appendix I** have been added, an erroneous link to ~~Appendix H~~ has been removed.

Section 6.2 Baseline Study Assessments

- 12-lead ECGs **need to be completed pre-dose and 5 minutes apart, if QTcF prolongation is identified assess electrolyte levels (including potassium and magnesium) as clinically indicated.**

Section 6.4.1 Induction Phase

- **Serum pregnancy test once per cycle during the induction phase**

Section 6.4.1.1 Cycle 1, Days 1, 3 and 5

- Physical examination and vital signs **(Days 3 and 5)**
- ECOG performance status **(Days 3 and 5)**
- Removed duplicative statement: ~~Confirmation and/or placement of central venous catheter or peripherally inserted central catheter~~

Section 6.4.1.4 Cycle 1 Day 21 (Response assessment)

- **ECG**

Section 6.4.1.6 Cycle 2, Days 1 and 3 (re-induction, only applicable if patient achieves PR with recovery bone marrow after Cycle 1)

- Physical examination and vital signs **(Days 3 and 5)**
- ECOG performance status **(Days 3 and 5)**

Section 6.4.1.9

- **ECG**

Section 6.4.2 Consolidation Phase **(If applicable)**

- **Serum pregnancy test once per cycle during the consolidation phase**

Section 6.4.2.1 Cycle 1, Day 1 and 3

- **ECG (Day 3)**

Section 6.4.2.3 Cycle 1 Days 14 and 21

- **ECG**

Section 6.4.2.4 Cycle 1 Day 35 (±7 days) (BM recovery)

- ~~Update of medical history~~

Section 6.4.2.5 Cycle 2, Days 1 and 3 **(if applicable)**

- **ECG (Day 3)**

Section 6.4.2.7 Cycle 2 Days 14 and 21

- **ECG**

Section 6.4.4 Maintenance Phase

- **Serum pregnancy test once every 3 cycles during the maintenance phase**

Section 6.4.4.1 Cycles 1-24, Days 1 and 15

- ECG and QTcF assessment (if QTcF ≤470 msec, continue quizartinib; if QTcF >470 msec, see Appendix F) ~~(Day 1 only)~~

Section 6.4.6 Long-Term Follow-up

- ~~"Underlying d~~**D**isease **response** assessment per ~~ASBMT/~~CIBMTR ~~disease~~ classification"

Section 6.5.3 12-Lead Electrocardiogram

- "**If QTcF prolongation develops from the time of initial screening to the day of quizartinib administration (i.e. Day +8 of induction), concomitant medications and electrolytes should be assessed for a reversible cause. ECGs may be repeated daily for up to 3 days from the original start date to assess for correction and to meet the eligibility criteria to administer quizartinib (see Section 3.2).**"

Section 6.5.5 Pregnancy Testing

- **Serum Pregnancy tests are also required prior to the start of each cycle during the induction and consolidation phases, during maintenance phase a serum pregnancy test will obtained once every 3 cycles.**

Section 6.5.12 Minimal Residual Disease Assessment

- MRD analysis of *FLT3*-ITD mutations will occur with all recovery marrows with induction and consolidation cycles (if applicable) Day~~+ 28~~**35** (+/- 7 days) post-cellular therapy intervention (if applicable), as well as with bone marrow biopsies obtained during the maintenance phase. To monitor for molecular recurrence of disease, BM biopsies and aspirates will be collected at **Day 24 (+/- 3 days)** Cycles 3, 6, 12, and 24 during the maintenance phase.

Section 7.2 Quizartinib Treatment Duration

- Prior to initiation (≤24 h**our**) ~~an~~ ECG**s in triplicate** will be obtained to assess QTc**F.**

Section 7.5.1 Precautions and Risks Associated with Quizartinib

- "QTc Prolongation, Torsades de Pointes" has been revised to refect an updated IB.
- **Additionally in greater than 10% of patients infection, decreased appetite, abdominal pain, painful swelling, sores in the mouth, rash, asthenia or fatigue, pyrexia, peripheral edema, abnormal hepatic function, mineral deficiency, enzyme deficiency, anemia, and weight loss were reported.**
- **Differentiation Syndrome** has been added as a risk associated with Quizartinib.

Section 7.5.2 Precautions and Risks Associated with CPX-351

- Because of the potential for serious adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with CPX-351. ~~and for at least 2 weeks after the last dose~~

Section 8.1, Table 2 and Table 3

- **For AE toxicity management with concomitant strong CYP3A4 inhibitor, the dose of quizartinib will not be reduced lower than 20 mg/day refer to Table 2 for more information).**

- The title to table 2 has been updated to state "Induction **and Consolidation** Phase' Footnotes in Table 2 and Table 3 have been corrected to link to the appropriate reference.

Section 8.2.1 Criteria and Procedures for Dose Modifications due to QTcF prolongation

- "Electrolytes (potassium~~, calcium~~, and magnesium) should be checked and supplementation given to correct any values outside the normal range."
- The following text has been added
    - **"In addition, hypomagnesemia and hypokalemia abnormalities can affect the QT interval. Upon identification of QTcF prolongation, it is advised to assess the subject's electrolytes (including potassium and magnesium) and manage** per local institutional standards."
    - "**If QTcF is > 450, evaluation of concomitant medications are advised as well as a magnesium level is advised to assess for potential etiologies. Repeating ECGs daily for up to 3 days can occur to determine if the QTcF improves to allow administration of quizartinib."**

Section 8.3.1 Criteria and Procedures for Dose Interruptions and Adjustments of CPX-351

- Criteria and Procedures for Dose Interruptions and Adjustments of CPX-351 has been moved to Section 8.3.1 for readability.

Section 9.1 Complete Response (CR)

- Patients with a CR but with residual MRD positivity (CR MRD^{+}) are classified **as indicated**.

Section 9.7 Event-free Survival (EFS)

- The following sentence has been added "**This calculation does not pertain to Long Term Follow-up data.**"

Section 10.5.1 Safety Review

- If ~~≥~~ ≥3 patients experience delayed neutrophil count recovery >56 days from the first day receiving the study regimen, defined as having a peripheral blood ANC <500/µL without evidence of residual disease by BM biopsy, or if ~~≥~~ ≥3 patients develop a non-hematologic toxicity, defined as a Grade 4 non-hematologic AE determined to be probably related to the combined treatment, then the study will be terminated

References

- **Sexauer A, Perl A, Yang X, Borowitz M, Gocke C, Trivikram R, et al. Terminal myeloid differentiation in vivo is induced by FLT3 inhibition in FLT3/ITD AML. Blood. 2012;120(20):4205-14.**

Appendix D Schedule of Assessments

- Added the word '**Day'** to the first row of the table for readability
- Clarified assessment: Physical examination, **height (screening only), and weight.**
- The assessment 'TTE or MUGA scan' has been updated to remove the Day 1 of consolidation phase assessment.

- Serum pregnancy tests have been added to start of each cycle during the induction and consolidation phases, during maintenance phase a serum pregnancy test will obtained once every 3 cycles.
    - Footnote 'J' has been revised to include: "**Serum Pregnancy tests are also required prior to the start of each cycle during the induction and consolidation phases, during maintenance phase a serum pregnancy test will obtained once every 3 cycles**."
- Footnote 'D' has been revised to include the following: "**If the patient is on quizartinib prior to HCT or CT intervention, quizartinib should be discontinued 7 days prior if a conditioning therapy is utilized**"

Appendix F Management of Quizartinib-Associated Adverse Events

- Addition of additional instructions for Grade 2 QTcF prolongation: "**Following dose reduction, the quizartinib/placebo dose may be resumed at the previous level in the next cycle if the QTcF has decreased to within 30 msec of baseline or <450 msec but subject must be monitored closely for QT prolongation for the first cycle at the increased dose**."
- **Differentiation Syndrome** management instructions have been added.

AML 48 PROTOCOL SYNOPSIS

Title of Study:	A Phase II Study Assessing CPX-351 (Vyxeos™) with Quizartinib for the Treatment of Relapsed or Refractory FLT3-ITD Mutation-Positive AML	
Development Innovations Study Number:	AML 48	
Sponsor:	Sarah Cannon Development Innovations, LLC	
Study Duration:	The total duration of the study is planned to be approximately 4 years.	**Phase of Study:** II
Number of Study Centers:	This study will be conducted at approximately 5 sites in the United States.	
Number of Patients:	Approximately 34 patients are planned to be enrolled in this study.	
Objectives:	**Primary Objectives** The primary objectives of this study are to: • Determine the safety and tolerability of CPX-351 (cytarabine:daunorubicin liposome complex) with quizartinib in patients with relapsed or refractory fms-like tyrosine kinase 3 (FLT3)-internal tandem duplication (ITD) mutation-positive acute myeloid leukemia (AML). • Determine the overall complete morphologic (per World Health Organization) and molecular remission rate of CPX-351 and quizartinib in patients with relapsed or refractory FLT3-ITD mutation-positive AML. **Secondary Objectives** The secondary objectives of this study are to: • Define the time to absolute neutrophil count and platelet count recovery • Define the number of patients proceeding to an allogeneic stem cell transplant (alloHCT) • Determine time to disease progression or duration of response • Determine event-free survival • Determine overall survival • Define the percentage of patients who develop late responses • Define the number of patients who can receive consolidation and maintenance therapy on this study • Define the treatment-related mortality rate of this combination • Determine the percentage of patients who achieve a PR or molecular complete remission (CR) • Determine the mean elapsed time for patients to achieve molecular CR • Determine whether quizartinib is tolerable after alloHCT or donor lymphocyte infusion.	
Study Design:	This is a multi-center, non-randomized, open-label, two-part prospective Phase II clinical trial in patients with relapsed or refractory FLT3-ITD mutation-positive AML. The study is designed to assess the safety and tolerability as well as the efficacy of administering CPX-351 (cytarabine:daunorubicin liposome complex) with quizartinib, a second-generation FLT3 inhibitor. The plan for administration is divided into three phases: induction, consolidation, and maintenance. Approximately 34 patients are planned to be screened and enrolled.	

	A total of 10 patients will be enrolled in the safety lead-in, which is designated as Part 1 of the study. If ≥8 patients meet the pre-specified safety parameters, an additional 24patients will be enrolled in Part 2 of the study. All patients will be assessed for response.
Study Drug, Dose, and Mode of Administration:	Induction phase: CPX-351 (daunorubicin 44 mg/m^2 IV and cytarabine 100 mg/m^2 IV) will be given on Days 1, 3, and 5 followed by 30 mg quizartinib by mouth (PO) once daily on Days 8-21. Patients with an incomplete response, but a >50% reduction in the blast count/cellularity ratio compared to the most recent bone marrow (BM) biopsy prior to treatment, should receive one additional cycle of induction therapy (re-induction) with CPX-351 (daunorubicin 44 mg/m^2 IV and cytarabine 100 mg/m^2 IV) on Days 1 and 3 only. Re-induction will begin after a 72-hour washout period from the last dose of quizartinib. During re-induction, treatment with quizartinib will resume on Day 6 and continue through Day 21. Any patient with neutropenia or thrombocytopenia lasting ≥56 days from the initiation of CPX-351 will not receive consolidation and will instead proceed to the maintenance phase. Consolidation phase: At the Investigator's discretion, patients who achieve CR and do not proceed to an alloHCT or other CT intervention will proceed to the consolidation phase beginning 7 days (± 7) after neutrophil recovery (ANC >1000/µL). Administer up to 2 consolidation cycles of CPX-351 (daunorubicin 29 mg/m^2 IV and cytarabine 65 mg/m^2 IV) on Days 1 and 3. Begin quizartinib 30 mg PO once daily on Days 6-21. Maintenance phase: Maintenance dosing of quizartinib will begin at 30 mg/day on Days 1-14, and if there are no non-hematologic Grade ≥3 toxicities, the quizartinib dose will increase to 60 mg/day on Day 15. The maintenance phase is a 28-day cycle beginning 7 days (± 7) after neutrophil recovery (ANC >1000/µL) from the consolidation phase or induction phase. Patients will receive quizartinib once daily for a total of 24 cycles or until disease relapse
Inclusion Criteria :	1. Written informed consent form (ICF), according to local guidelines, signed by the patient or by a legal guardian prior to the performance of any study-related screening procedures 2. Male and female patients between ≥18 and <80 years old 3. Patients with the following types of AML with >5% blasts: − Relapsed FLT3-ITD mutation-positive AML, diagnosed by BM biopsy with FLT3 mutation by polymerase chain reaction (PCR) − Refractory FLT3-ITD mutation-positive AML, diagnosed by BM biopsy with FLT3 mutation by PCR − Relapsed or refractory FLT3-ITD mutation-positive AML after hematopoietic cell transplantation (HCT), diagnosed by BM biopsy with FLT3 mutation by PCR − Relapsed or refractory AML with de novo FLT3-ITD mutation, diagnosed by BM biopsy with FLT3 mutation by PCR − Relapsed or refractory AML after HCT with de novo FLT3-ITD mutation, diagnosed by BM biopsy with FLT3 mutation by PCR 4. First-line therapy must have contained a standard induction chemotherapy (e.g., 7+3, FLAG-IDA, FLAG, CLAG, MEC, hypomethylating agent with venetoclax) with or without receiving a prior FLT3 inhibitor (e.g., midostaurin) or multi-tyrosine kinase inhibitor (e.g., sorafenib). Patients who relapsed after an alloHCT are included, except patients with active graft-versus-host disease (GVHD) requiring >10 mg prednisone. 5. Patients must be able to swallow and retain oral medication.

	6. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1, or 2 (Appendix A) 7. Adequate renal and hepatic parameters (aspartate aminotransferase [AST], alanine aminotransferase [ALT] ≤2.5 institutional upper limit of normal [ULN]; total bilirubin ≤2.0 institutional ULN; serum creatinine [Cr] ≤2.0). In patients with suspected liver infiltration, ALT can be ≤5 institutional ULN.
Exclusion Criteria :	1. Acute promyelocytic leukemia (t[15;17]) 2. Female patients who are lactating or have a positive serum pregnancy test during the screening period. Female patients of childbearing potential who are not willing to employ highly effective birth control (as defined in Appendix C) from screening to 6 months following the last dose of CPX-351 and/or quizartinib. 3. Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential must use condoms plus a spermicidal agent during the study treatment period and for 6 months following their last dose of CPX-351 and/or quizartinib, and must not father a child during this period.(refer to Appendix C). 4. Evidence of active and uncontrolled bacterial, fungal, parasitic, or viral infection. Infections are considered controlled if appropriate therapy has been instituted and, at the time of screening, no signs of active infection progression are present. This is assessed by the site clinicians, including an infectious disease consulting physician, if requested by the Principal Investigator (PI), regarding adequacy of therapy. These infections include, but are not limited to: - Known human immunodeficiency virus (HIV) infection - Active hepatitis B or C infection with rising transaminase values - Active tuberculosis infection 5. History of hypersensitivity to cytarabine, daunorubicin, or an FLT3 inhibitor 6. Any patients with known significant impairment in gastrointestinal (GI) function or GI disease that may significantly alter the absorption of quizartinib . 7. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol. 8. Uncontrolled or significant cardiovascular disease, including any of the following: - Bradycardia of less than 50 beats per minute, unless the patient has a pacemaker - QTcF interval using Fridericia's correction factor (QTcF) interval prolongation, defined as >450 msec at screening and prior to first administration of quizartinib. - Diagnosis of or suspicion of long QT syndrome (including family history of long QT syndrome) - Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg - History of clinically relevant ventricular arrhythmias (i.e., ventricular tachycardia, ventricular fibrillation or Torsades de pointes)

	– History of second or third degree heart block without a pacemaker – Right bundle branch and left anterior hemiblock (bifascicular block), complete left bundle branch block – Ejection fraction <50% by transthoracic echocardiogram (TTE) or multigated acquisition (MUGA) scan – History of uncontrolled angina pectoris or myocardial infarction within 6 months prior to Screening 9. History of New York Heart Association Class 3 or 4 heart failure 10. Prior anthracycline (or equivalent) cumulative exposure ≥368 mg/m2 daunorubicin (or equivalent) 11. Any serious underlying medical condition that, in the opinion of the Investigator or Medical Monitor, would impair the ability to receive or tolerate the planned treatment 12. Patients with inadequate pulmonary function will be excluded. Inadequate pulmonary function is defined as requiring supplemental O2 or diffusing capacity of the lungs for carbon monoxide [DLCO] <40%. 13. Active acute or chronic GVHD requiring prednisone >10 mg or equivalent corticosteroid daily

Statistical Methodology:	A response rate (CR + CR with incomplete hematologic recovery [Cri]) of ≥50% is targeted, with 40% or less considered unacceptable. This is assumed to be an acceptable estimate based on CR + CRi/CRp of 48.2% reported with quizartinib monotherapy in a relapsed or refractory patient with FLT3-ITD AML (Cortes et al, 2019). Of note, prior FLT3-targeting inhibitor exposure is permitted on this study. However, patients receiving a prior FLT3-targeting inhibitor were excluded in the QUANTUM-R study. Expected CR+CRi in relapsed or refractory patients receiving standard intensive or non-intensive salvage chemotherapy harboring an FLT3 mutation is 27%. The estimated response in those with relapsed/refractory FLT3-ITD AML receiving CPX-351 alone cannot be estimated. However, in a poor-risk EPI patient population, CR+CRi was reported as 39.3% (Cortes et al 2015). However, FLT3-ITD mutation presence was not utilized in the generation of EPI prognostication, and those with FLT3-ITD mutation could in fact have a reduced response within all EPI risk groups. Thus, the expected response must be based upon the QUANTUM-R study of those receiving standard salvage options harboring a FLT3-ITD mutation. In the safety lead-in, 10 patients will be enrolled to receive CPX-351 with quizartinib. If >3 patients experience delayed neutrophil count recovery >56 days from the first day on the study regimen, or delayed thrombocytopenia recovery >56 days from the first day on the study regimen, or if >3 patients develop a non-hematologic toxicity, defined as a Grade 4 non-hematologic adverse event determined to be probably related to the combined treatment, or a Grade 4 neutropenia, then the study will be terminated. Assuming safety parameters are met, the first 10 patients will be followed for response in Part 2 of the study. The null hypothesis that the overall response rate (ORR, defined as CR + CRi) is ≤27% will be tested against a one-sided exact alternative ORR of 50% at a target significance level of 0.05. A sample size of 30 evaluable patients achieves 80% power if the true overall response rate is ≥50%. The null hypothesis will be rejected if 13 or more responses are observed in 30 evaluable patients. In order to allow for a non-evaluable rate of 10%, a total of 34 patients will be enrolled in the study.

LIST OF ABBREVIATIONS

AE	Adverse event
AESI	AE of special interest
alloHCT	Allogeneic hematopoietic cell transplantation
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ASBMT	American Society for Blood and Marrow Transplantation
AST	Aspartate aminotransferase
BM	Bone marrow
CBC	Complete blood count
CFR	Code of Federal Regulations
CIBMTR	Center for International Blood and Marrow Transplant Research
CNS	Central nervous system
CR	Complete remission/response
Cr	Creatinine
CRi	Complete remission/response with incomplete hematologic recovery
CT	Cellular therapy
Development Innovations	Sarah Cannon Development Innovations
DLI	Donor lymphocyte infusion
DOR	Duration of response
DS	Differentiation Syndrome
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	Event-free survival
EPI	European Prognostic Index
FDA	Food and Drug Administration
FLT3	Fms-like tyrosine kinase-3
GCP	Good Clinical Practice
GI	Gastroinestinal
GVHD	Graft-versus-host disease
HCT	Hematopoietic cell transplantation
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ISF	Investigator study file
IT	Intrathecal
ITD	Internal tandem duplication

MRD	Minimal residual disease
MUGA	Multigated acquisition scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next-generation sequencing
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
P-gp	P-glycoprotein
PHI	Protected health information
PI	Principal Investigator
PICC	Peripherally inserted central catheter
PO	By mouth (orally)
PR	Partial response
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAR	Suspected adverse reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TdP	Torsades de pointes
TEAE	Treatment-emergent AE
TKD	Tyrosine kinase domain
TTE	Transthoracic echocardiogram
ULN	Upper limit of normal
USPI	US package insert
WHO	World Health Organization

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1. INTRODUCTION

1.1 Background

Fms-like tyrosine kinase-3 (FLT3) mutations are identified in approximately 30% of patients with acute myeloid leukemia (AML) and confer a poor prognosis, with an estimated 5-year overall survival (OS) of approximately 32% (Kottaridis et al 2001). FLT3 is a receptor tyrosine kinase for the cytokine Flt3 ligand (FLT3L) and is expressed on hematopoietic progenitor cells. The FLT3L transduces signals that promote proliferation and survival, and mutations of the FLT3 receptor present as two general types: internal tandem duplications (ITDs) near the receptor juxtamembrane domain, and single amino acid substitutions within the activation loop of the tyrosine kinase domain (TKD) (Levis 2013). While FLT3-TKD mutations do not confer the same poor prognosis as FLT3-ITD mutations, their presence is associated with resistance to chemotherapy (Whitman et al 2001, Takahashi et al 2016).

In both young and old AML patients, approximately 60% will achieve a complete response to standard induction chemotherapy for acute myeloid leukemia (Rowe 2009). While response to initial therapy is comparable among all patients, in those who relapse with a FLT3 mutation, response to re-induction is significantly less compared to non-FLT3 mutated patients, with a complete response (CR) of 22-24% in two analyses (Ravandi et al 2010, Wagner et al 2011). Due to the poorer prognosis of patients with FLT3 mutation-positive AML, allogeneic hematopoietic cell transplant (alloHCT) is indicated in the first CR (CR1) (Pratz et al 2017). In patients who are able to proceed to hematopoietic cell transplantation (HCT), the relapse rate after transplant is higher compared to non-FLT3 mutated patients (Fleischmann et al 2017, Deol et al 2016). Additional therapeutic options are necessary for those who fail to achieve a CR1 or for those whose disease relapses.

Recent Phase III data combining the first-generation FLT3 inhibitor midostaurin with standard induction daunorubicin and cytarabine identified a statistically significant improvement in median OS with the FLT3 inhibitor of 74.7 months (95% confidence interval [CI] 31.5, not reached) compared to placebo with 25.6 months (95% CI 18.6, 42.9) (Stone et al 2017). Midostaurin as well as sunitinib and sorafenib are multi-kinase inhibitors with non-FLT3 targets. Second-generation FLT3 inhibitors, including quizartinib and gilteritinib, are more selective and potent, with a possible reduction in the development of FLT3-TKD mutations that may confer resistance to FLT3 inhibition therapy (Smith et al 2012, Perl et al 2017).

1.2 Quizartinib

Quizartinib is a potent and selective class III fms-like tyrosine kinase 3 (FLT3)-ITD inhibitor under active investigation (Kampa-Schittenhelm et al 2013). A Phase I dose-finding study using quizartinib as monotherapy in refractory AML demonstrated an overall response rate (ORR) of 30% and a median duration of response (DOR) of 13.3 weeks (Cortes et al 2013). All grades of toxicities included nausea (16%), prolonged QT interval (12%), vomiting (11%), and dysgeusia (11%). In a historical control analysis, patients with refractory AML receiving standard salvage therapy or those who relapsed after stem cell transplantation were evaluated. Those receiving quizartinib achieved a CR of 43% compared to 11% in those who did not receive the agent, and a

statistically significant improvement in OS was identified (Hills et al 2015). In a randomized Phase II study using quizartinib as monotherapy in patients with at least one second-line therapy or after an HCT, ORR was 47% (Schiller et al 2014).

1.3 CPX-351

Other novel therapies for the treatment of AML have demonstrated improved outcomes. CPX-351 is a cytarabine:daunorubicin liposomal complex demonstrated to improve the induction response rate to 66.7%, compared to 51.2% for in patients with previously untreated AML receiving 7+3 (**7** days of standard dose cytarabine and **3** days of daunorubicin) (Lancet et al 2014). A Phase III analysis in patients with secondary AML aged 60 - 75 demonstrated a CR of 47.7% with CPX-351 versus 33.3% with standard regimens (Medeiros et al 2016). In addition, a significant improvement in OS was seen in a subset of patients who proceeded to HCT (Lancet et al 2016a).

CPX-351 was also evaluated in patients who failed to respond to 7+3 induction. Four out of 10 patients who received CPX-351 alone achieved a morphologic CR (Lancet et al 2010). The explanation may be that intracellular 5:1 drug concentration of cytarabine:daunorubicin with cytarabine achieves a half-life of 31.1 hours and daunorubicin 21.9 hours. Compared to standard dosing of free-drug, the half-life of cytarabine and daunorubicin was 13 hours (Lim et al 2010, Tardi et al 2009, Fathi et al 2013, Feldman et al 2011). CPX-351 alone compared to investigator's choice for re-induction in refractory AML achieved a morphologic CR rate of 49.4% compared to 40.9%, although this did not meet a pre-defined statistically significant benefit for 1 year OS (Cohen 2007, Cortes et al 2015). However, a sub-group analysis demonstrated that poor-risk European Prognostic Index (EPI) patients receiving CPX-351 had a statistically significant improvement in OS compared to poor-risk EPI patients receiving standard re-induction therapies (Cortes et al 2015). Patients with FLT3 mutations are not factored into the EPI risk stratification, although associated patient characteristics in those with FLT3-ITD AML, including time of recurrence and non-favorable cytogenetics, could place this patient population into poor-risk EPI, suggesting a benefit with CPX-351 (Breems et al 2005).

The poor prognosis in patients with FLT3 mutation-positive AML who have relapsed or failed to respond to induction therapy is an unmet medical need that warrants investigation with novel therapeutic combinations.

1.4 Rationale for the Study

The purpose of this study is to assess the safety, tolerability, and efficacy of the combination of CPX-351 and quizartinib. The ability to deliver a stable liposomal formulation of cytarabine:daunorubicin packaged at a 5:1 molar ratio combined with continuous potent FLT3 inhibition is hypothesized to potentially provide disease control. A recent pre-clinical study demonstrated synergistic activity when CPX-351 was dosed with an FLT3 inhibitor. This synergy was demonstrated when the FLT3 inhibitor was administered after CPX-351, but not when the FLT3 inhibitor was administered simultaneously or prior to CPX-351 (Edwards et al 2017). Investigation of this novel combination in the relapsed/refractory population is reasonable in this high-risk disease population. Since OS in AML is directly related to achieving

disease control (a molecular CR), the goal of this study is to determine if novel cytoreduction with CPX-351 combined with targeted FLT3 inhibition can achieve improved disease control over what has been previously reported in the literature.

Patients with relapsed or refractory FLT3 mutation-positive AML have limited options. A goal of this treatment is to achieve adequate disease control that may potentially allow a bridge to consolidative cellular therapeutic intervention (e.g., HCT or donor lymphocyte infusion [DLI]) for some patients. In patients who are not candidates for or decline a cellular intervention, the treatment goal is to achieve definitive disease control with the combination of CPX-351 and quizartinib followed by quizartinib maintenance.

In all patients with AML who relapse after an alloHCT, those who receive treatment with chemotherapy, DLI, and/or a second alloHCT achieve a CR rate of 29% with a 5-year OS ≤11% in those who relapse less than 2 years after first transplant and ≤31% for those who relapse 2 years or more after first transplant (Weisdorf et al 2013). Currently, it is believed that many relapsed FLT3 mutation-positive AML patients would not have received an FLT3 inhibitor as part of a prior regimen. Novel chemotherapy in combination with a targeted FLT3 inhibitor may provide a significant improvement in survival for this patient population compared to the current standard of care.

1.5 Risks and Benefits

The risks associated with the study derive from the novel combination of CPX-351 with quizartinib. The most anticipated side effect is pancytopenia, with potentially prolonged neutropenia and thrombocytopenia compared to standard induction or salvage chemotherapy. In a randomized study in AML patients, CPX-351 demonstrated a median time to absolute neutrophil count (ANC) ≥1000 of 36 days compared to 32 days with standard cytarabine and daunorubicin (7+3). In addition, there was a statistically significant increase in Grade 3 or Grade 4 infections. However, infection-related mortality has not been demonstrated. In the same study, platelet count recovery to >100,000 was 37 days compared to 28 days in those receiving 7+3. Quizartinib in combination with cytarabine and daunorubicin was associated with 21% of study participants showing Grade ≥3 toxicity for both neutropenia and thrombocytopenia. However, there was no prolonged period of pancytopenia, suggesting that the proposed novel combination of CPX-351 and quizartinib may not contribute to a longer period of myelosuppression than what is expected with CPX-351 alone. Grade 3 and higher febrile neutropenia was identified in 63.5% of patients receiving CPX-351 alone (Lancet et al 2014) and in 47% of patients receiving quizartinib alone (Altman et al 2018).

CPX-351 contains daunorubicin, an anthracycline that has a known association with cardiomyopathy at threshold doses of 550 mg/m^2. Patients will be excluded if their cumulative dose of an anthracycline exceeds this threshold. To date, quizartinib has not been associated with cardiomyopathy or a reduction in the ejection fraction. Quizartinib has been associate with QT prolongation in a dose dependent manner. In study AC220-007 (Quantum-R) in the relapse/refractory FLT3+ AML population, Eight (3.3%) subjects in the quizartinib arm had ECG QTcF values >500 ms (Grade 3 QTcF) by central ECG reading. (Quizartinib Investigator Brochure 2020. CPX-351 has not been associated with significant QTc prolongation (CPX-351 US package insert [USPI]). For this study, these cardiac risk factors will need to be monitored

and accounted for independently. Dose modifications for QTcF prolongation will be based upon pre-specified monitoring and criteria (see Section 8).

All grades of gastrointestinal toxicities associated with CPX-351 were similar to standard induction 7+3, with the most frequent being nausea (47%), diarrhea/colitis (45%), mucositis (44%), and constipation (40%). However, Grade 3 and higher gastrointestinal toxicities were less than 10% (Lancet et al 2016b). In Phase I/II investigations, quizartinib was found to be associated with all grades of nausea (16%), vomiting (11%), and diarrhea (18%) (Cortes et al 2013, Schiller et al 2014).

Given that the toxicities identified with each agent have minimal overlap, it is hoped that the novel combination will not result in the potentiation of the toxicity of either agent alone. A potential beneficial effect of this combination may be the protective effect of quizartinib on normal hematopoietic progenitor cells after exposure to chemotherapy. If dosed sequentially following CPX-351, this may attenuate the effects that CPX-351 has on healthy stem cells without compromising the effect on the leukemic cells (Taylor et al 2017. This potential benefit of the novel combination will be measured based on the timing of myeloid count recovery and comparing this data to data from prior CPX-351 studies.

It is assumed that there are four patient groups who may derive benefit on study for relapsed or refractory FLT3 mutation-positive AML. The first group includes patients who have primary refractory FLT3 mutation-positive AML and who fail first-line therapy with routine induction regimens with or without an FLT3 inhibitor. The second group includes patients with FLT3 mutation-positive AML who have relapsed after HCT. In both scenarios, the study intervention will likely act as a bridge to either an HCT or a DLI. The third group includes patients with relapsed FLT3 mutation-positive AML who were excluded from or declined alloHCT. In this patient population, the FLT3 inhibitor would continue as maintenance therapy. The final group of patients includes those who acquire an FLT3 mutation at relapse. This occurs more frequently in patients with epigenetic-modifying gene mutations at diagnosis (IDH1/2, DNMT3A, TET2) (Shih et al 2002, Wakita et al 2013). Depending on the management choice at the initial diagnosis and initial CR, the last clinical scenario may be a bridge to a first or second HCT or to a DLI.

1.6 Hypothesis

The purpose of this study is to explore the safety, tolerability and efficacy of CPX-351 with quizartinib in patients with FLT3 mutated AML. The investigators hypothesize:

The combination of liposomal nanomolar cytarabine:daunorubicin (CPX-351) with quizartinib, a second-generation FLT3 inhibitor, will be safe, tolerable and enhance the tumor response in patients with FLT3-mutated AML who have relapsed or whose tumor did not respond to standard and other therapeutic regimens.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are to:

- Determine the safety and tolerability of CPX-351 with quizartinib in patients with relapsed or refractory FLT3-ITD mutation-positive AML.
- Determine the overall complete morphologic (per World Health Organization) and molecular remission rate of CPX-351 and quizartinib in patients with relapsed or refractory FLT3-ITD.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Define the time to ANC and platelet count recovery
- Define the number of patients proceeding to an alloHCT
- Determine time to progressive disease (PD) or DOR
- Determine event-free survival (EFS)
- Determine OS
- Define the percentage of patients who develop late responses
- Define the number of patients who can receive consolidation and maintenance therapy on this study
- Define the treatment-related mortality rate of this combination
- Determine the percentage of patients who achieve a PR or molecular CR
- Determine the mean elapsed time for patients to achieve molecular CR
- Determine whether quizartinib is tolerable after alloHCT or DLI

2.3 Endpoints

2.3.1 Primary Endpoints

- Response rate determination:
  - Complete remission (CR) defined as a complete morphologic response with complete blood count recovery ANC ≥1000/µL and platelet count ≥100,000/µL), per the revised International Working Group response criteria (Cheson et al 2003) .
  - Complete remission with minimal residual disease (CR with MRD): Achievement of a complete morphologic CR with persistent disease detected by flow or molecular MRD analysis.
  - A complete morphologic response with an incomplete blood count recovery ([CRi] ANC <1000/µL and/or platelet count <100,000/µL), per the revised International Working Group response criteria (Cheson et al 2003). Patients will be further divided into MRD^+ and MRD^- subgroups.

- A partial response (PR) is defined as having persistence of disease, with a ≥50% decrease in the blast percentage with or without the presence of FLT3-ITD mutations.

2.3.2 Secondary Endpoints

- Time to ANC recovery >56 days (≥500/μL) and platelet count recovery>56 days (≥50,000/μL)
- Number of patients proceeding to an alloHCT
- Time to PD or DOR
- EFS
- OS

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria

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

1. Written informed consent form (ICF), according to local guidelines, signed by the patient or by a legal guardian prior to the performance of any study-related screening procedures
2. Male and female patients between ≥18 and <80 years old
3. Patients with the following types of AML with >5% blasts:
   - Relapsed FLT3-ITD mutation-positive AML, diagnosed by bone marrow (BM) biopsy with FLT3 mutation by polymerase chain reaction (PCR)
   - Refractory FLT3-ITD mutation-positive AML, diagnosed by BM biopsy with FLT3 mutation by PCR
   - Relapsed or refractory FLT3-ITD mutation-positive AML after HCT, diagnosed by BM biopsy with FLT3 mutation by PCR
   - Relapsed or refractory AML with de novo FLT3-ITD mutation, diagnosed by BM biopsy with FLT3 mutation by PCR
   - Relapsed or refractory AML after HCT with de novo FLT3-ITD mutation, diagnosed by BM biopsy with FLT3 mutation by PCR
4. First-line therapy must have contained a standard induction chemotherapy (e.g., 7+3, FLAG-IDA, FLAG, CLAG, MEC, hypomethylating agent with venetoclax) with or without receiving a prior FLT3 inhibitor (e.g., midostaurin) or multi-tyrosine kinase inhibitor (e.g., sorafenib). All patients who relapsed after an alloHCT are included, except patients with active graft-versus-host disease (GVHD) requiring >10 mg prednisone.
5. Patients must be able to swallow and retain oral medication.

6. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1, or 2 (Appendix A)
7. Adequate renal and hepatic parameters (aspartate aminotransferase [AST], alanine aminotransferase [ALT] ≤2.5 institutional upper limit of normal [ULN]; total bilirubin ≤2.0 institutional ULN; serum creatinine [Cr] ≤2.0). In patients with suspected liver infiltration, ALT can be ≤5 institutional ULN.

3.2 Exclusion Criteria

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

1. Acute promyelocytic leukemia (t[15;17])
2. Female patients who are lactating or have a positive serum pregnancy test during the screening period. Female patients of childbearing potential who are not willing to employ highly effective birth control (as defined in Appendix C) from screening to 6 months following the last dose of CPX-351 and/or quizartinib.
3. Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential must use condoms plus a spermicidal agent during the study treatment period and for 6 months following their last dose of CPX-351 and/or quizartinib, and must not father a child during this period.(refer to Appendix C)
4. Evidence of active and uncontrolled bacterial, fungal, parasitic, or viral infection. Infections are considered controlled if appropriate therapy has been instituted and, at the time of screening, no signs of active infection progression are present. This is assessed by the site clinicians, including an infectious disease consulting physician, if requested by the Principal Investigator (PI), regarding adequacy of therapy. These infections include, but are not limited to:
    - Known human immunodeficiency virus (HIV) infection
    - Active hepatitis B or C infection with rising transaminase values
    - Active tuberculosis infection
5. History of hypersensitivity to cytarabine, daunorubicin, or an FLT3 inhibitor
6. Any patients with known significant impairment in gastrointestinal (GI) function or GI disease that may significantly alter the absorption of quizartinib
7. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol
8. Uncontrolled or significant cardiovascular disease, including any of the following:
    - Bradycardia of less than 50 beats per minute, unless the patient has a pacemaker
    - QTcF interval using Fridericia's correction factor (QTcF) interval prolongation, defined as >450 msec at screening andprior to first administration of quizartinib.

- Diagnosis of or suspicion of long QT syndrome (including family history of long QT syndrome)
- Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg
- History of clinically relevant ventricular arrhythmias (i.e., ventricular tachycardia, ventricular fibrillation or Torsades de pointes)
- History of second or third degree heart block without a pacemaker
- Right bundle branch and left anterior hemiblock (bifascicular block), complete left bundle branch block
- Ejection fraction <50% by transthoracic echocardiogram (TTE) or multigated acquisition (MUGA) scan
- History of uncontrolled angina pectoris or myocardial infarction within 6 months prior to Screening

9. History of New York Heart Association Class 3 or 4 heart failure (Appendix B)
10. Prior anthracycline (or equivalent) cumulative exposure ≥368 mg/m^2 daunorubicin (or equivalent)
11. Any serious underlying medical condition that, in the opinion of the Investigator or Medical Monitor, would impair the ability to receive or tolerate the planned treatment.
12. Patients with inadequate pulmonary function will be excluded. Inadequate pulmonary function is defined as requiring supplemental O_2 or diffusing capacity of the lungs for carbon monoxide [DLCO] <40%.
13. Active acute or chronic GVHD requiring prednisone >10 mg or equivalent.

3.3 Discontinuation from Study Treatment

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

- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the Investigator's discretion)
- Inability of the patient to comply with study requirements
- Patient requests to discontinue treatment, but agrees to finish study procedures
- Patient withdraws consent from the study and is discontinued from the study
- Non-compliance/lost to follow-up
- Pregnancy and breastfeeding
- Further participation would be injurious to the patient's health or well-being, in the Investigator's medical judgment

- The study is terminated by the Sponsor, Sarah Cannon Development Innovations ("Development Innovations") or the Institutional Review Board (IRB)

After discontinuation from protocol treatment, patients must be followed for adverse events (AEs) for 30 days after their last dose of study drug. All new AEs occurring during this period must be reported and followed at the site until resolution for AEs attributed to the study medication(s).

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4. PATIENT REGISTRATION

The patient must willingly consent to participate after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, treatment alternatives, side-effects, risks, and discomforts. Institutional Review Board (IRB) approvals of this protocol and consent form are required. Eligible patients who wish to participate in the study will be enrolled into the study.

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

5. STUDY DESIGN

This is a multi-center, non-randomized, open-label, two-part prospective Phase II clinical trial in patients with relapsed or refractory FLT3-ITD mutation-positive AML. The study is designed to assess the safety and tolerability as well as the efficacy of administering CPX-351 (cytarabine:daunorubicin liposome complex) with quizartinib, a second-generation FLT3 inhibitor. The plan for administration is divided into three phases: induction, consolidation, and maintenance. Approximately 34 patients are planned to be screened and enrolled. Patient participation is expected to be 4 years.

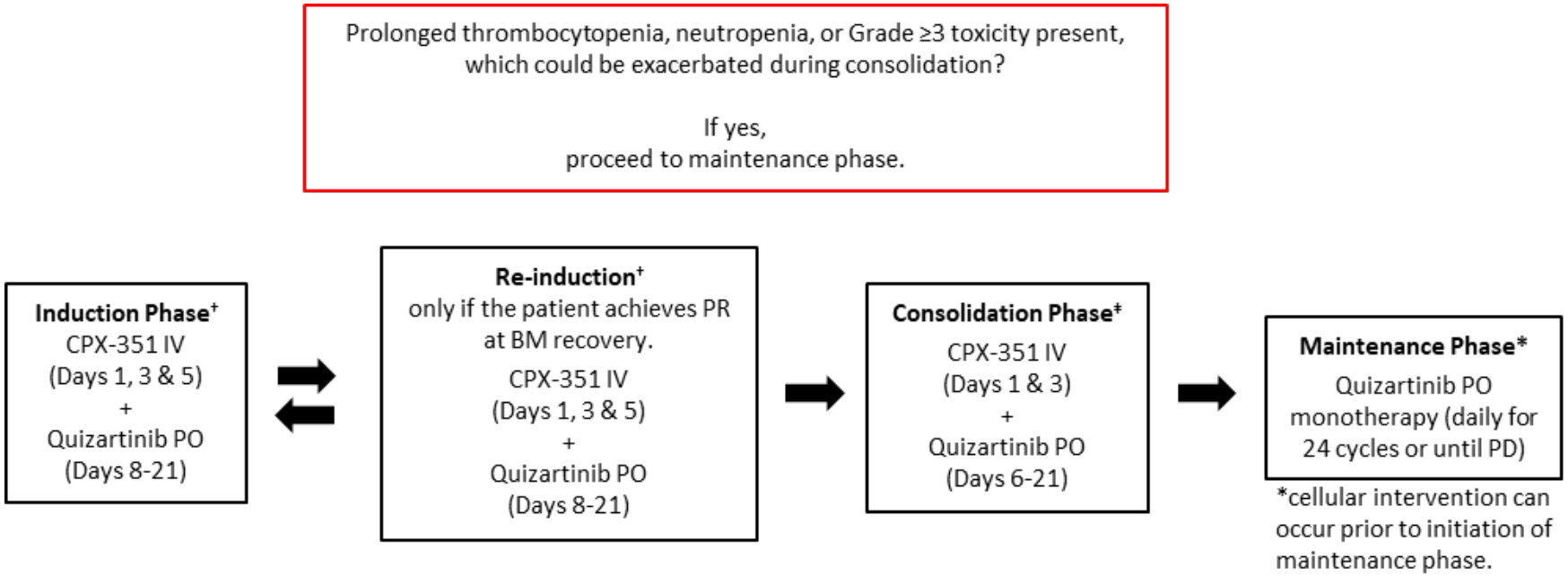
A total of 10 patients will be enrolled in the safety lead-in. The safety lead-in portion of the study is designated as Part 1. If >3 patients experience delayed neutrophil count recovery >56 days from the first day on the study regimen, or delayed thrombocytopenia recovery >56 days from the first day on the study regimen, or if >3 patients develop a non-hematologic toxicity, defined as a Grade 4 non-hematologic adverse event determined to be probably related to the combined treatment, or a Grade 4 neutropenia, then the study will be terminated.

Assuming safety parameters are met, the first 10 patients will be followed for response in the Part 2 of the study. An additional 24 patients will be enrolled in Part 2 of the study (induction, consolidation and maintenance). All patients will be assessed for response.

Patients who fail to respond to therapy will be followed until a new therapy is instituted. . Patients who experience an AE that results in the discontinuation of study treatment will be

followed until resolution/stabilization for AEs attributed to the medication. Outcomes for all patients will be assessed for 24 months from the date of last treatment.

Figure 1 Study Schema



*All treatment phases follow a 28-day cycle. Induction and re-induction consist of: CPX-351 (liposomal daunorubicin 44 mg/m2 IV and cytarabine 100 mg/m2 IV) + quizartinib 30 mg PO QD. The maintenance phase: begin quizartinib 30 mg PO QD on Days 1-14. If there are no toxicities and QTcF is maintained ≤450 msec, increase dose to 60 mg QD on Day 15.
†For one cycle
‡For up to two cycles

5.1 Assignment of Treatment

All patients will receive CPX-351 with quizartinib according to the treatment plan (Section 5.2).

5.2 Treatment Plan

The plan for administration is divided into three phases: induction, consolidation, and maintenance. In patients who decline HCT or cellular therapy (CT) intervention or are ineligible, the patient would proceed through induction, consolidation, and maintenance.

Patients who achieve a CR (CR or CRi) after induction(s), will proceed to consolidation followed by the maintenance phase. In patients who achieve a PR, re-induction can occur for one additional cycle followed by consolidation and maintenance phases if a CR is achieved with re-induction. In patients who achieve a CR or PR after induction and/or consolidation and an HCT or other CT intervention (e.g., HCT or DLI) is indicated, maintenance therapy would be initiated no earlier than Day 30 after the HCT or CT intervention. If the patient is on quizartinib prior to HCT or CT intervention, quizartinib should be discontinued 7 days prior if a conditioning therapy is utilized. If proceeding to a CT intervention without conditioning therapy (e.g., DLI), quizartinib should be discontinued one day prior to CT intervention.

Response assessment will occur by BM biopsy/aspirate 21 days (±2 days) from CPX-351 induction and/or re-induction therapy as well as Day 35 (±7 days) during induction and consolidation therapy (within 4 days after neutrophil as defined as a peripheral ANC ≥500/µL for 24 hours). In the event of a delayed neutrophil recovery, defined as having a peripheral ANC <500/µL at Day 42 from the first day of CPX-351 treatment, a BM biopsy will be taken to assess persistent disease. During the maintenance phase, subsequent response assessments by BM biopsy/aspirate will be done on Day 24 (± 3 days) of a 28-day treatment cycle during Cycles 3, 6, 12, and 24.

5.2.1 Treatment Location

5.2.1.1 Inpatient procedures

Patients will be admitted to the clinic as inpatients to start induction therapy. If the Day +21 (±2 days) BM aspirate shows no evidence of disease, the patient is stable based on PI assessment, and close outpatient follow-up is available, then the patient can be discharged with three weekly lab checks (Monday, Wednesday, and Friday) and weekly provider visits.

5.2.1.2 Outpatient procedures

Consolidation cycles may be administered on an outpatient basis with IV infusion of CPX-351 and three weekly lab checks (Monday, Wednesday, and Friday) and weekly provider visits. Maintenance cycles are all outpatient with monthly lab/provider visits.

5.2.2 Induction Phase

Treatment consists of CPX-351 (liposomal daunorubicin 44 mg/m^2 IV and cytarabine 100 mg/m^2 IV) on Days 1, 3, and 5 followed by quizartinib (30 mg by mouth [PO] once daily) on Days 8-21. If there is a PR at the recovery BM biopsy, patients may be re-treated with one additional induction therapy (re-induction) with CPX-351 (daunorubicin 44 mg/m^2 IV and cytarabine 100

mg/m^2 IV) on Days 1 and 3. Quizartinib (30 mg by PO once daily) will resume on Day 6 and continue through Day 21. If re-induction is required, a minimum 72-hour period is necessary between the dose of quizartinib on Day 21 and the administration of CPX-351 with re-induction.

If it is believed by the PI and/or sub-investigator that a patient with prolonged Grade ≥3 toxicity after the induction phase would be likely to experience additional toxicities during the consolidation phase, the patient could bypass the consolidation phase and proceed to a cellular intervention or the maintenance phase. Any patient with neutropenia or thrombocytopenia lasting ≥56 days from the initiation of CPX-351 will not receive consolidation and will instead proceed to the maintenance phase.

5.2.3 Consolidation Phase

Patients who achieve a CR and do not proceed to an alloHCT or other CT intervention will proceed from induction to the consolidation phase beginning 7 days (±7 days) after neutrophil recovery (ANC >1000/µL), receiving up to 2 consolidation cycles consisting of CPX-351 (daunorubicin 29 mg/m^2 IV and cytarabine 65 mg/m^2 IV) on Days 1 and 3. Quizartinib therapy (30 mg PO once daily) will start on Day 6 and continue through Day 21.

After the first consolidation cycle, if it is believed by the PI and/or sub-investigator that a patient with prolonged Grade ≥3 toxicity would have additional adverse toxicities during the second consolidation phase, and/or there is CRi with persistent ANC <1000/µL and/or platelets <50,000/µL more than 14 days from the recovery marrow assessment, then the patient could proceed to a cellular intervention or the maintenance phase.

5.2.4 Maintenance Phase

The maintenance phase consists of 28-day cycles. Patients will receive quizartinib once daily for a total of 24 cycles or until disease relapse. Maintenance dosing of quizartinib will begin at 30 mg PO once daily on Days 1-14, and if there are no non-hematologic Grade ≥3 toxicities and QTcF is maintained ≤450 msec, the quizartinib dose will increase to 60 mg/day on Day 15. If consolidation therapy is not advised at all or if only 1 cycle of consolidation is advised based on prolonged toxicities, maintenance therapy will begin 7 days (±7) after neutrophil recovery (ANC >1000/µL) from the consolidation phase or induction phase.

Patients who proceed to alloHCT or other CT intervention after consolidation will resume quizartinib maintenance no earlier than Day 30 from the intervention or transplant. If ≥2 CT interventions (e.g., repeat DLI) are planned after maintenance, a 28-day hold is acceptable, with resumption of quizartinib with the next cycle. If the patient is on quizartinib prior to HCT or CT intervention, quizartinib should be discontinued 7 days prior if a conditioning therapy is utilized. If proceeding to a CT intervention without conditioning therapy (e.g., DLI), quizartinib should be discontinued one day prior to CT intervention.

5.3 Concomitant Medications

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

5.3.1 Permitted Concomitant Medications

Patients with hematologic malignancies receiving therapy are at an increased risk for infections, and antiviral, antifungal, and antibacterial prophylactic agents should be administered per institutional guidelines. It is considered routine practice to administer acyclovir or a similar anti-viral to reduce the risk of herpes simplex virus (HSV) or varicella zoster virus (VZV) reactivation, voriconazole or other anti-fungal agent to reduce the risk of a fungal infection, and an antibiotic such as levofloxacin to reduce the risk of neutropenic fever. It is important to note that many antifungal agents require a dose modification of quizartinib. Electrocardiograms (ECGs) will need to be performed on patients who receive medications that cause significant QTc prolongation.

Additional supportive care measures (e.g., anti-emetics for nausea, anti-motility agents for diarrhea management) are permitted at the Investigator's discretion. Concomitant treatments and/or procedures that are required to manage a patient's medical condition during the study will be recorded in the electronic case report form (eCRF).

5.3.2 Prohibited Concomitant Medications

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

- Other investigational therapies (e.g., chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or hormonal therapy not required by this protocol) should not be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study.
- Herbal preparations/medications are not allowed throughout the study unless approved by the Investigator. Herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using herbal medications 7 days prior to first dose of study drug.
- While receiving quizartinib, concomitant medications that prolong the QT/QTc interval are prohibited except when regarded by the Investigator as essential for patient care (Appendix F and Appendix I).
- Strong CYP3A4 inhibitors are not prohibited, although quizartinib dose adjustments are required. Weak or moderate CYP3A4 inhibitors, such as fluconazole, may be used without dose reduction (Appendix H).
    - When treatment with a strong CYP3A4 inhibitor is initiated, reduce quizartinib one dose level (60 mg to 30 mg or 30 mg to 20 mg)
    - A patient taking a strong CYP3A4 inhibitor at enrollment will begin quizartinib treatment at 20 mg/day. The dose will be escalated to 30 mg/day at Day 15 of the maintenance phase if the QTcF interval is ≤450 msec prior to or at the Day 14 ECG evaluation.
- Concomitant strong or moderate CYP3A4 inducers are prohibited (Appendix H).
- Concomitant agents that prolong QTc are prohibited (Appendix I)

If quizartinib is co-administered with drugs that inhibit P-glycoprotein (P-gp) or are substrates of P-gp, increased concentrations of quizartinib are possible and caution should be exercised. The co-administration of P-gp inhibitors and inducers with quizartinib should be avoided if possible.

6. STUDY ASSESSMENTS AND EVALUATIONS

6.1 Overview

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

6.2 Baseline Study Assessments

The following information will be collected and procedures will be performed for each patient at a baseline study assessment. This screening assessment will take place following written informed consent (see Section 13.3) and within 7 days prior to initiating study treatment.

- Medical history and demographics
- Physical examination (including height [screening only] and weight)
- Vital signs (pulse, resting blood pressure, respiratory rate, and body temperature)
- ECOG performance status (Appendix A)
- 12-lead ECG need to be completed pre-dose and 5 minutes apart, if QTcF prolongation is identified assess electrolyte levels (including potassium and magnesium) as clinically indicated.
- Concomitant medication review
- Complete blood count (CBC) including differential count
- Chemistry panel: sodium (Na), potassium (K), phosphorus (PO4), chloride (Cl), Cr, calcium (Ca), bicarbonate (CO2), AST, ALT, alkaline phosphatase (ALP), total bilirubin, lactate dehydrogenase (LDH), uric acid, glucose, and blood urea nitrogen (BUN)
- Urinalysis
- Serum pregnancy test for women of child-bearing potential
- Review of viral studies: hepatitis serology (Hepatitis B surface antigen and antibody and Hepatitis C antibody), HIV-1, 2
- Underlying disease assessment per American Society for Blood and Marrow Transplantation/Center for International Blood and Marrow Transplant Research (ASBMT/CIBMTR) disease classification (Appendix E)
- BM biopsy and aspiration with FLT3 mutation testing via PCR
- TTE or MUGA scan
- Central line placement: peripherally inserted central line (PICC) or port

- Baseline signs and symptoms

6.3 Central Nervous System (CNS) Prophylaxis

Patients with a history of CNS involvement of leukemia, with monocytic differentiation, or with a WBC >40,000 cells/µL should receive a lumbar puncture using either intrathecal (IT) methotrexate or cytarabine, following site-specific standard operating procedures during the first induction cycle of CPX-351 with quizartinib.

The CNS prophylaxis regimen may be modified by the attending physician in consultation with the PI as clinically indicated. No further IT chemotherapy is required in this study if there is no evidence of disease. However, additional administrations, per the treating physician or per institutional standard operating procedures, are permitted.

In patients who have CNS disease involvement, IT chemotherapy should continue every 4 days (±1 day) until disease clearance, followed by every 7 days (±2 days) for 2 additional administrations. Thereafter, administer IT chemotherapy every 28 days (±7 days) for at least 12 cycles.

6.4 Study Assessment Timing

The treatment period begins on the day the patient receives the first administration of CPX-351. Dates for study visits and assessments will be determined based upon the first day of treatment and should occur based on the timing parameters outlined in this protocol.

6.4.1 Induction Phase

- Serum pregnancy test once per cycle during the induction phase

6.4.1.1 Cycle 1, Days 1, 3 and 5

- Physical examination and vital signs (Days 3 and 5)
- ECOG performance status (Days 3 and 5)
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panel
- CPX-351 administration (Days 1, 3, and 5)

6.4.1.2 Cycle 1, Day 8

- Physical examination and vital signs
- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panel

- ECG and QTc assessment
- Quizartinib daily on Days 8-21 (if QTcF ≤450 msec)

6.4.1.3 Cycle 1 Day 14

- Physical examination and vital signs
- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panel
- ECG and QTc assessment (if QTcF >470 msec, see Appendix F)

6.4.1.4 Cycle 1 Day 21 (Response assessment)

- Physical examination and vital signs
- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panel
- BM biopsy and aspirate with FLT3 mutation testing via PCR
- ECG

6.4.1.5 Cycle 1 Day 35 (± 7 days) (BM recovery)

- Physical examination and vital signs
- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panel
- BM biopsy and aspirate for MRD assessment via next-generation sequencing (NGS) and FLT3 mutation testing via PCR

6.4.1.6 Cycle 2, Days 1 and 3 (re-induction, only applicable if patient achieves PR with recovery bone marrow after Cycle 1)

- Physical examination and vital signs (Days 3 and 5)
- ECOG performance status (Days 3 and 5)
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panels

- CPX-351 administration (Days 1 and 3)

6.4.1.7 **Cycle 2, Day 6**

- Physical examination and vital signs
- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panels
- ECG and QTcF assessment (if QTcF ≤470 msec, resume quizartinib)
- Quizartinib (daily on Days 6-21, if QTcF ≤470 msec)

6.4.1.8 **Cycle 2 Day 14**

- Physical examination and vital signs
- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panel
- ECG and QTc assessment (if QTcF >470 msec, see Appendix F)

6.4.1.9 **Cycle 2 Day 21 (Response assessment)**

- Physical examination and vital signs
- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panel
- BM biopsy and aspirate with FLT3 mutation testing via PCR
- ECG

6.4.1.10 **Cycle 2 Day 35 (±7) (BM recovery)**

- Physical examination and vital signs
- ECOG performance status
- AE monitoring
- Concomitant medication review

- CBC and clinical chemistry panel
- BM biopsy and aspirate for MRD assessment via next-generation sequencing (NGS) and FLT3 mutation testing via PCR

6.4.2 Consolidation Phase (If applicable)

- Patients who achieve CR and do not receive an alloHCT or other CT intervention will receive up to 2 cycles of consolidation therapy with CPX-351 and quizartinib.
- Serum pregnancy test once per cycle during the consolidation phase

6.4.2.1 Cycle 1, Day 1 and 3

- Physical examination and vital signs
- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panel
- CPX-351 (Days 1 and 3)
- ECG (Day 3)

6.4.2.2 Cycle 1, Day 6

- Physical examination and vital signs
- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panel
- ECG and QTcF assessment (if QTcF ≤470 msec, resume quizartinib on Day 4)
- Quizartinib (begin daily until Day 21)

6.4.2.3 Cycle 1 Days 14 and 21

- ECG

6.4.2.4 Cycle 1 Day 35 (±7 days) (BM recovery)

- Physical examination and vital signs
- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panel
- BM biopsy and aspirate for MRD assessment via next-generation sequencing (NGS) and FLT3 mutation testing via PCR

6.4.2.5 **Cycle 2, Days 1 and 3 (if applicable)**

- Physical examination and vital signs
- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panel
- CPX-351 (Days 1 and 3)
- ECG (Day 3)

6.4.2.6 **Cycle 2, Day 6**

- Physical examination and vital signs
- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panel
- ECG and QTcF assessment (if QTc ≤470 msec, resume quizartinib)
- Quizartinib (begin daily until Day 21)

6.4.2.7 **Cycle 2 Days 14 and 21**

- ECG

6.4.2.8 **Cycle 2, Day 35 (±7 days)**

- Physical examination and vital signs
- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panel
- BM biopsy and aspirate with FLT3 mutation testing via PCR
- MRD assessment with BM biopsy and aspirate via NGS

6.4.3 **alloHCT or other CT intervention (within the 30-60 day time period between consolidation and maintenance treatment)**

- Physical examination and vital signs

- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panel
- BM biopsy and aspirate with FLT3 mutation testing via PCR (~ Day 30)
- MRD assessment with BM biopsy and aspirate via NGS

6.4.4 Maintenance Phase

The maintenance phase consists of quizartinib monotherapy once daily in 28-day cycles for a total of 24 cycles or until disease relapse. Maintenance dosing of quizartinib PO will begin at 30 mg/day on Days 1-14, and if there are no toxicities and QTcF is maintained ≤450 msec, the dose will increase to 60 mg/day on Day 15. The following procedures and tests will be performed at these visits:

- Serum pregnancy test once every 3 cycles during the maintenance phase

6.4.4.1 Cycles 1-24, Days 1 and 15

- Physical examination and vital signs
- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panel
- BM biopsy and aspirate with FLT3 MRD NGS mutation testing (Day 24 ±3 days) at Cycle 3, 6, 12 and 24
- ECG and QTcF assessment (if QTcF ≤470 msec, continue quizartinib; if QTcF >470 msec, see Appendix F)

6.4.5 End of Treatment/Early Termination Visit

Patients will complete the study at the time of PD, if they withdraw consent, if they withdraw due to an AE, or at the time the study is terminated. If either study treatment or patients are discontinued, the reason will be recorded in the eCRF and source document. Patients who are removed from treatment for reasons other than death or disease progression (PD) are considered to be patients who have terminated early. Reasons for discontinuation include one of the following: AEs, protocol violation, patient withdraws consent, patient is lost to follow-up, administrative reasons (including study closure), death, or other. Patients who complete or discontinue from the study should have the following study completion/early withdrawal evaluations performed as soon as possible after the day of study completion/early withdrawal.

- Physical examination and vital signs

- ECOG performance status
- AE monitoring
- Concomitant medication review
- CBC and clinical chemistry panels
- BM biopsy and aspirate with FLT3 mutation testing, if applicable
- ECG and QTcF assessment, if applicable

Patients prematurely discontinuing from the study must be followed for AE and concomitant medication use for 30 days following the last administration of study drugs or until resolution/stabilization of an ongoing AE attributed to the medication.

Patients who discontinue from the study may be treated with other therapies at the discretion of the Investigator.

6.4.6 Long-Term Follow-up

A formal end-of-study visit will be performed every 6 months for 2 years post-study treatment. The following procedures and tests will be done:

- Disease response assessment per CIBMTR classification (Appendix E)
- Survival status

6.5 Study Assessments

6.5.1 Medical History and Demographics

A complete medical history will be taken. Information to be documented includes demographics, prior medical illnesses and conditions, prior surgical procedures, date and stage of original diagnosis and details of prior chemotherapy/radiotherapy administered and other treatments for cancer (including type of drugs, dosages, schedule or administration, response and response duration).

6.5.2 Physical Examinations (Including Performance Scale and Vital Signs)

A complete physical examination will be done at baseline, at each visit, at the end-of-treatment visit, and long-term follow-up visit as well as at the discretion of the Investigator. Examinations will include documentation of height (at screening only), weight, vital signs, and ECOG performance status (Appendix A). Any abnormal or clinically significant findings from the physical examination must be recorded on the appropriate eCRF page.

6.5.3 12-Lead Electrocardiogram

Triplicate ECGs recording will be performed according to Appendix D and at the discretion of the Investigator. Each will be performed with the patient in a supine position having rested in this position for at least 5 minutes before the reading. If QTcF prolongation develops from the time of initial screening to the day of quizartinib administration (i.e. Day +8 of induction), concomitant medications, and electrolytes should be assessed for a reversible cause. ECGs may

be repeated daily for up to 3 days from the original start date to assess for correction and to meet the eligibility criteria to administer quizartinib (see Section 3.2).

6.5.4 Cardiac Echocardiogram

A TTE or MUGA will be obtained upon enrollment, prior to initiation of treatment, and within 1 week prior to consolidation treatment (Day 1).

6.5.5 Pregnancy Testing

In women of child-bearing potential, a serum beta human chorionic gonadotropin pregnancy test must be done 72 hours prior to the start of treatment. Serum Pregnancy tests are also required prior to the start of each cycle during the induction and consolidation phases, during maintenance phase a serum pregnancy test will obtained once every 3 cycles.

6.5.6 Laboratory Assessments

Laboratory samples (CBC, clinical chemistry, urinalysis, and virology) are to be collected as outlined in Appendix D. Laboratory results will be graded using NCI CTCAE Version 5.0.

6.5.7 FLT3 Mutation PCR Testing

The presence of the FLT3-ITD mutation will be detected using PCR from bone marrow aspiration samples collected with all planned BM samples. Next-generation sequencing of MRD by FLT3-ITD mutational analysis will be performed with all planned BM biopsies, excluding screening and the Day +21 induction response assessment. The presence of FLT3-ITD for inclusion is defined as positive if the PCR assay detects tandem duplication at 3% or higher.

6.5.8 Response and Activity Assessments

See Section 6.5.11 and Section 9.

6.5.9 Adverse Event Assessments

Information regarding the occurrence of AEs, including infections, will be collected from the time the patient signs the ICF throughout their participation in the study, including a period of 30 days after the last dose of study drug. Adverse event severity will be determined using the CTCAE Version 5.0 grading scale. See Section 11 for more details.

6.5.10 Prior and Concomitant Medications

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

6.5.11 Bone Marrow Aspirates and Biopsies

Response assessment by BM biopsies and aspirates will be collected at Day 21 (±2 days) of induction (and re-induction therapy, if applicable), as well as at the time of count recovery after CPX-351 + quizartinib, defined as obtaining a BM biopsy within 4 days of having an ANC >500µL for ≥24 hours (at Day 35 [±7 days] during induction and consolidation therapy). Bone marrow biopsies and aspirates will also be collected after Cycles 3, 6, 12, and 24 in the maintenance phase. Thereafter, assessment of disease status will be at the discretion of the primary treating hematologist/oncologist.

All biopsies will include monitoring for FLT3 mutation by PCR. Additional studies, including fluorescence in situ hybridization (FISH), cytogenetics, and/or molecular analyses, should be obtained based upon known mutations at the discretion of the physician.

6.5.12 Minimal Residual Disease Assessment

Invivoscribe, Inc. will use an assay to determine MRD status after treatment with quizartinib and CPX-351. Minimal residual disease is defined as the minimal traceable persistence of leukemia after treatment.

The assay uses PCR amplification of exons 14 and 15 of FLT3. The PCR primers contain gene-specific regions that are coupled with NGS adaptors designed to identify ≥1 *FLT3*-ITD-containing cell in 10,000 BM cells. An MRD^- status will be defined as all results from BM that are negative for the presence of residual clonal cells (<1 *FLT3*-ITD-containing cell in 10,000 bone marrow cells). A MRD^+ status will be defined as all results from whole blood or BM that are positive for residual clonal cells (≥1 *FLT3*-ITD-containing cell in 10,000 bone marrow cells). In addition to MRD positivity or negativity, MRD level will be monitored, and the number of residual clonal cells per 10,000 cells will be recorded as well as the total number of cells evaluated in the sample (Levis 2018b).

MRD analysis of *FLT3*-ITD mutations will occur with all recovery marrows with induction and consolidation cycles (if applicable) Day 35 (+/- 7 days) post-cellular therapy intervention (if applicable), as well as with bone marrow biopsies obtained during the maintenance phase. To monitor for molecular recurrence of disease, BM biopsies and aspirates will be collected at Day 24 (+/- 3 days) Cycles 3, 6, 12, and 24 during the maintenance phase.

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

7.1 Quizartinib

Investigational Product	Dosage Form and Strength	Manufacturer
Quizartinib	20- and 30-mg tablets	Daiichi Sankyo

7.2 Quizartinib Treatment Duration

Patients will receive oral quizartinib once daily, on Days 8-21 of the induction cycle and Days 6-21 of re-induction, if necessary. Administration cannot begin earlier than 24 hours from the last administration of CPX-351. During the consolidation cycles(s), quizartinib begins on Day 6.

Prior to initiation (≤24 hour), ECGs in triplicate will be obtained to assess QTcF. If the QTcF is ≤450 msec, treatment with quizartinib may proceed (see Section 8). Patients proceeding to an additional cycle of induction as well as those proceeding to consolidation therapy must ensure the FLT3 inhibitor has not been administered before a 4-5 half-life reduction of quizartinib, equivalent to 3 days from the date of last administration.

After induction and consolidation cycles, patients will start maintenance therapy with quizartinib, continuing treatment on Days 1-28 of a 28-day cycle for a total of 24 maintenance cycles.

7.2.1 Labeling, Packaging, and Supply of Quizartinib

Quizartinib tablets will be supplied in high density polyethylene (HDPE) bottles with child-resistant caps.

All study drugs must be kept in a secure place under appropriate storage conditions. Storage conditions for quizartinib are included in the USPI.

7.2.2 Preparation and Administration of Quizartinib

Quizartinib is administered orally. Each 20-mg tablet contains 20 mg quizartinib dihydrochloride (17.7 mg free base) and 200 mg HPβCD. The 20-mg tablets also contain microcrystalline cellulose, magnesium stearate, and Opadry® white film coating. Each 30-mg tablet contains 30 mg quizartinib dihydrochloride (26.5 mg free base) and 300 mg HPβCD. The tablets also contain microcrystalline cellulose, magnesium stearate, and Opadry® yellow film coating.

Preparation and administration instructions will be provided in the quizartinib Investigator's Brochure (IB) and in the USPI.

7.3 CPX-351 Treatment Duration

Patients will be administered CPX-351 (daunorubicin 44 mg/m^2 IV and cytarabine 100 mg/m^2 IV) on Days 1, 3, and 5 of the induction cycle. As noted in Section 5, re-induction with CPX-351 (daunorubicin 44 mg/m^2 IV and cytarabine 100 mg/m^2 IV) on Days 1 and 3 should occur in patients with an incomplete response in the recovery marrow biopsy, defined as a >50% reduction in the blast count to cellularity ratio compared to the most recent BM biopsy prior to induction. Following induction, a total of 2 cycles of consolidation will occur with CPX-351 (daunorubicin 29 mg/m^2 IV and cytarabine 65 mg/m^2 IV) administered on Days 1 and 3.

7.3.1 Labeling, Packaging, and Supply of CPX-351

Daunorubicin and cytarabine liposome for injection is supplied as a sterile, preservative-free, purple, lyophilized cake, in a single-dose vial. Each CPX-351 vial contains 44 mg daunorubicin and 100 mg cytarabine. Store unreconstituted CPX-351 vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in an upright position. The vial should be stored in its original carton to protect it from light.

7.3.2 Preparation and Administration of CPX-351

Intravenous infusion of CPX-351 (cytarabine:daunorubicin liposome complex) **requires a central venous catheter or a peripherally inserted central catheter.** CPX-351 is administered over 90 minutes.

Preparation and administration instructions will be provided in the CPX-351 (cytarabine:daunorubicin liposome complex) IB and in the USPI.

7.4 Accountability for All Study drugs

The PI (or designee) is responsible for accountability of all used and unused study drug supplies at the site. Development Innovations representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

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

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

7.5 Toxicity of Study Treatments and Study Regimens

7.5.1 Precautions and Risks Associated with Quizartinib

A Phase I dose-finding study using quizartinib as monotherapy in refractory AML demonstrated an ORR of 30% and a median DOR of 13.3 weeks (Cortes et al 2013). All grades of toxicities included nausea (16%), prolonged QT interval (12%), vomiting (11%), and dysgeusia (11%). In a randomized Phase II study using either 30 mg or 60 mg of quizartinib as monotherapy, the patients taking the 30 mg daily dose were found to have a lower incidence of Grade ≥2 QTcF prolongation (11%) compared to those who received 60 mg daily (17%). For both dosing groups, other toxicities included diarrhea (18%) and febrile neutropenia (16%) (Schiller et al 2014). Additionally in greater than 10% of patients infection, decreased appetite, hemorrhagic events, abdominal pain, painful swelling, sores in the mouth, rash, asthenia or fatigue, pyrexia, peripheral edema, abnormal hepatic function, mineral deficiency, enzyme deficiency, anemia, and weight loss were reported (Quizartinib Investigator Brochure 2020).

Myelosuppression

Serious AEs of myelosuppression (e.g., febrile aplasia, neutropenia, BM hypocellularity, lymphocytopenia, anemia, thrombocytopenia, and pancytopenia) have been observed, which may result in infections or hemorrhage. Resulting infections (particularly, but not exclusively, fungal and other opportunistic infections, Gram-negative bacterial infections, and bacteremia/septicemia/sepsis) or hemorrhage (e.g., epistaxis, hemoptysis, melena, gastrointestinal bleeding, and hemorrhage intracranial) may be severe, including fatal outcomes. Reports of infection have often been in the context of neutropenia, fever, or both.

QTc Prolongation, Torsades de Pointes

Quizartinib is associated with QTc interval prolongation. QTc interval prolongation may increase the risk of ventricular arrhythmias or TdP.

Regarding review of clinical events potentially associated with QT prolongation (Refer to IB for details):

Completed studies:

- Of the 241 patients treated with quizartinib in the completed Phase 3 clinical study in adults with relapsed or refractory AML (Study AC220-007), 3.3% were found to have a QTcF interval greater than 500 msec, and 12.4% had an increase from baseline QTcF greater than 60 msec based on central review of ECG data; there were no cases of TdP, cardiac arrest or sudden death reported at the recommended doses (i.e., 30 mg or 60 mg). . In the remaining studies (AC220-002, 2689 CL 2004, CP0001, and 2689-CL-0005): there was 1 subject with TdP (in a phase 2 study while receiving a dose of 90mg; the event resolved after discontinuation of quizartinib, see below for details), 5 subjects with cardiac arrest/cardio-respiratory arrest, and 3 subjects with ventricular tachycardia reported. Overall, after individual review of these events with two external cardiac electrophysiology experts, the 1 event of TdP was associated with QT prolongation, and in 1 of the events of cardiac arrest, a potential arrhythmia event cannot be excluded.
- In the ongoing blinded AC220-A-U302 study in which quizartinib is given in combination with chemotherapy, 6 events of cardiac arrest/cardio-respiratory arrest (5 fatal and 1 non-fatal) and 1 event of sudden death have been reported with quizartinib (See IB section 5.3.6 for further details). Of these, one fatal and one non-fatal cardiac arrest events were due to ventricular fibrillation, and both occurred in the setting of Grade 3 or 4 hypokalemia. These events highlight the importance of monitoring and correcting electrolytes, such as potassium, that may result in QT prolongation as an independent risk factor. The remaining events of fatal cardiac arrest occurred in the setting of other significant concurrent disease (severe sepsis /septic shock, multi-organ failure) with complications and no subject had evidence of QT prolongation at the time of the event (all reported QTcF were <450ms).

Quizartinib should be not be used in subject with long QT syndrome. Quizartinib should be used with caution in patients who are at significant risk of developing QTc interval prolongation. These include patients with uncontrolled or significant cardiovascular disease, congestive heart failure, , hypokalemia and hypomagnesemia, and history of clinically relevant ventricular arrhythmias or TdP and patients receiving concomitant drugs known to prolong the QTc, interval. Electrolytes should be maintained in the normal range. Concomitant use with CYP3A inhibitors may increase quizartinib exposure, and therefore, the dose of quizartinib should be reduced. Specific instructions regarding ECG monitoring, quizartinib dose interruption/reduction and restrictions of concomitant use of other QTc-prolonging drugs are provided in Section 8 and Appendix F.

Quizartinib is an I_{Ks} inhibitor and is associated with QTc prolongation in a dose-dependent manner. As an I_{Ks} inhibitor, quizartinib differs from other agents that can prolong QTc which are I_{Kr} inhibitors. Inhibition of either I_{Ks} and/or I_{Kr} potassium channels may carry increased risk of cardiac events. In Study AC220-007, TEAEs of ECG QT prolonged were reported for 26.6% of patients in the quizartinib arm and 2.1% of patients in the salvage chemotherapy arm. Ten patients (4.1%) had a Grade 3 event, and no patient had a Grade 4 event. In the quizartinib arm, TEAEs of ECG QT prolonged were associated with study drug interruption for 11 (4.6%) patients, dose reduction for 23 (9.5%) patients, and study drug discontinuation for 2 (0.8%) patients (both Grade 2 events).

Eight (3.3%) patients in the quizartinib arm had ECG QTcF values >500 msec (Grade 3 QTcF) by central ECG reading. None of these patients had sequelae (e.g., associated ventricular arrhythmias), and all were able to either continue with the same dose of quizartinib or resume at the same or reduced dose after an interruption with no further occurrences of Grade 3 QTcF. There were no cases of cardiac arrest, sudden death, or TdP in the quizartinib arm.

Torsades de Pointes is an identified ADR for quizartinib. There was 1 case of TdP in a 63-year-old female patient in Study AC220-002 with history of atrial fibrillation. This patient was taking concomitant medications known to cause QT prolongation and/or increase quizartinib exposure. On Day 20 of quizartinib 90 mg therapy, QTcF was 543 msec (baseline: 418 msec) and a 15-beat episode of TdP was noted, which terminated spontaneously. It should be noted that this patient had Klebsiella bacteremia/sepsis with episodes of respiratory arrest prior to TdP and was also noted to have hypocalcemia (1.66 mmol/L; reference range: 2.10 to 2.55 mmol/L). Quizartinib was discontinued, and the event resolved the same day.

In review of all potential arrhythmia events associated with QT prolongation from the entire quizartinib program (and presented in IB v 14 Section 5.3.6), the following **notable** events, which occurred while on treatment with quizartinib, are summarized below:

- Completed Studies:):
    - A fatal **cardiocardiopulmonary** arrest occurred in a 39-year-old female patient with staph aureus sepsis on Day 40 when dosing of quizartinib monotherapy was 135 mg daily, increased 4 days prior to event with QTcF values were 471 msec, 459 msec, and 496 msec at 1 day, 3 days, and 4 days prior to the fatal event, respectively.
- Ongoing studies: (Ongoing study AC220-A-U302
    - A fatal cardiac arrest occurred in a 54-year-old female patient on Day 79 with ventricular fibrillation and Grade 3 hypokalemia on the preceding day. While the investigator assessed the event as not related, the Sponsor assessment was related.
    - A non-fatal cardiac arrest occurred in a 63-year-old female on Day 5 in the setting of Grade 4 hypokalemiaIn the ongoing blinded AC220-A-U302 study in which quizartinib is given in combination with chemotherapy, 6 events of cardiac arrest/cardio-respiratory arrest (5 fatal and 1 non-fatal) and 1 event of sudden death have been reported with quizartinib. Of these, one fatal and one non-fatal cardiac arrest events were due to ventricular fibrillation, and both occurred in the setting of Grade 3 or 4 hypokalemia. These events highlight the importance of monitoring and correcting electrolytes, such as potassium, that may result in QT prolongation as an independent risk factor. The remaining events of fatal cardiac arrest occurred in the setting of other significant concurrent disease (severe sepsis /septic shock, multi-organ failure) with complications and no subject had evidence of QT prolongation at the time of the event (all reported QTcF were <450ms).

One case of sudden death was reported with limited information in a 69-year-old male with history of hypertension and diabetes who died in his sleep 10 days after the last dose of

quizartinib on Day 111. The patient was last seen by the site on Day 100, and there were no adverse events reported from this visit. During the >3 month duration of the study, no other cardiac AE's were reported, and all QTcF were <480 msec. The investigator reported that the cause of death is most likely related to underlying AML.

These events highlight the importance of ECG monitoring, appropriate dosing and dose modifications for QTcF and concomitant use of strong CYP3A inhibitors, monitoring and correcting electrolytes, such as potassium, and magnesium, as electrolyte abnormalities are an independent risk factor.

A review of additional safety data inthe Investigator's Brochure did not identify new TEAEs in the TdP/QT Prolongation SMQ or additional patients with QTcF >450 msec.

Differentiation Syndrome

Quizartinib can cause terminal differentiation of AML blast cells in patients with relapsed or refractory disease (Sexauer et al 2012). Terminal differentiation of AML blast cells may be associated with the development of differentiation syndrome (DS) and may be life-threatening or fatal if not treated.

DS is a severe inflammatory reaction with increased capillary permeability. Symptoms of DS are dyspnea, hypoxia, fever, peripheral edema, hypotension, weight gain, pleuro-pericardial effusion, pulmonary infiltrated, acute renal failure, musculoskeletal pain, and hyperbilirubinemia, peripheral edema, hepatic, renal, or multi-organ dysfunction. Less commonly, DS might present with pulmonary hemorrhage or acute febrile neutrophilic dermatosis.

It is important to promptly recognize the signs and symptoms of DS and implement appropriate treatment. Patients with suspected DS should promptly start treatment with systemic glucocorticoids and hemodynamic monitoring until improvement (Quizartinib Investigator Brochure 2020).

7.5.2 Precautions and Risks Associated with CPX-351

- Cardiotoxicity

  The total cumulative dose of non-liposomal daunorubicin >550 mg/m^2 has been associated with an increased incidence of drug-induced congestive heart failure. In patients who received radiation therapy, the maximum tolerable lifetime dose is 400 mg/m^2. Calculate maximum lifetime exposure prior to each cycle as shown in Table 1.

Table 1 Cumulative Exposure of Daunorubicin per Cycle of CPX-351

Therapy	Daunorubicin per Dose	Number of Doses per Cycle	Daunorubicin per Cycle
First induction cycle	44 mg/m^2	3	132 mg/m^2
Second induction cycle	44 mg/m^2	2	88 mg/m^2
Each consolidation cycle	29 mg/m^2	2	58 mg/m^2

See dose modification/administration guidelines (Appendix G).

- Hemorrhage

12% Grade ≥3 (8% in control/7+3 arm), fatal non-disease associated CNS hemorrhage 2% (0.7% in control arm)

- Hypersensitivity

Known in patients receiving cytarabine and daunorubicin. See dose modification/administration guidelines (Appendix G).

- Tissue necrosis

Administer by central venous catheter

- Embryo-fetal toxicity

Counsel to avoid pregnancy, and to use contraception through 6 months after last administration of agent. Because of the potential for serious adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with CPX-351. In males, CPX-351 may cause infertility. In male patients wishing to conceive in the future, cryopreservation of sperm prior to administration is recommended.

- Cytopenias

Prolonged thrombocytopenia (<50 beyond Day 42) 28% (versus 12%) in induction and 25% (versus 16%) in consolidation; prolonged neutropenia (ANC <500 beyond Day 42) 17% (versus 3%) in induction and 10% (versus 3%) in consolidation. See dose modification/administration guidelines (Appendix G).

- Chemistry abnormalities

Hyponatremia (14%, 6% with consolidation), hypokalemia (9%, 6% with consolidation), hypoalbuminemia (7%, 2% with consolidation), hyperbilirubinemia (6%, 2% with consolidation), and elevated ALT (5%, 0% with consolidation); all were similar in comparison to 7+3.

The most common serious adverse reactions (incidence ≥5%) were dyspnea, myocardial toxicity, sepsis, pneumonia, febrile neutropenia, bacteremia and hemorrhage. Adverse reactions led to discontinuation of CPX-351 in 18% of patients (13% in the control arm).

The adverse reactions leading to discontinuation on the CPX-351 arm included prolonged cytopenias, infection, cardiotoxicity, respiratory failure, hemorrhage (GI and CNS), renal insufficiency, colitis, and generalized medical deterioration.

The most common adverse reactions (incidence ≥25%) in patients on the CPX-351 arm were hemorrhagic events, febrile neutropenia, rash, edema, nausea, mucositis, diarrhea, constipation, musculoskeletal pain, fatigue, abdominal pain, dyspnea, headache, cough, decreased appetite, arrhythmia, pneumonia, bacteremia, chills, sleep disorders, and vomiting.

8. DOSE MODIFICATIONS

If toxicity occurs, the toxicity will be graded using the NCI CTCAE Version 5, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

8.1 Criteria and Procedures for Dose Interruptions and Adjustments of Quizartinib

The following are reasons for quizartinib dose reduction or dosing interruption:

- Adverse event: QTcF prolongation, other non-hematologic toxicities, or myelosuppression
- Concomitant administration of a strong CYP3A4 inhibitor

Guidance on dose reductions and interruptions of quizartinib during the induction and consolidation phases as well as the maintenance phase are presented in Table 2 and Table 3, respectively.

The dose of quizartinib will not be reduced lower than 30 mg/day in any phase of the study (not lower than 20 mg/day for patients receiving strong CYP3A4 inhibitors. For AE toxicity management with concomitant strong CYP3A4 inhibitor, the dose of quizartinib will not be reduced lower than 20 mg/day refer to Table 2 for more information).

If quizartinib is interrupted, doses will not be made up.

Table 3 Dose Level Modifications – Induction and Consolidation Phases

Induction and Consolidation Phase				
Full Dose	**AE, no concomitant strong CYP3A4 inhibitor**	**Concomitant strong CYP3A4 inhibitor**	**AE and concomitant strong CYP3A4 inhibitor**	**QTcF prolongation**
30 mg/day	20 mg/day	20 mg/day	Interrupt[a]	See Section 8.2.1

[a]Refer to Appendix F for duration of interruption. Missed doses will not be made up.

Table 4 Dose Level Modifications – Maintenance Phase

Maintenance Phase					
	Full Dose	**AE, no concomitant strong CYP3A4 inhibitor**	**Concomitant strong CYP3A4 inhibitor**	**AE and concomitant strong CYP3A4 inhibitor**	**QTcF prolongation**
Days 1-14	30 mg/day	20 mg/day	20 mg/day	Interrupt[a]	See Section 8.2.1
Days 15 onward	60 mg/day	40 mg/day[b]	30 mg/day[c]	30 mg/day[d]	See Section 8.2.1

[a]Refer to Appendix Ffor duration of interruption. Missed doses will not be made up.

[b]Can be further reduced to 30 mg/day, if necessary

[c]Can be further reduced to 20 mg/day, if necessary

[d]Can be interrupted, if necessary

8.2 Management of Quizartinib-Associated Adverse Events

Management for quizartinib-associated AEs is located in Appendix F.

8.2.1 Criteria and Procedures for Dose Modification due to QTcF Prolongation

Electrolytes (potassium and magnesium) should be checked and supplementation given to correct any values outside the normal range. Concomitant medications should be reviewed to identify and, if appropriate, discontinue any medication with known QT prolonging effects (see Appendix F). In addition hypomagnesemia, hypokalemia, and hypomagnesemia abnormalities can affect the QT interval. Upon identification of QTcF prolongation, it is advised to assess the subject's electrolytes (including potassium and magnesium) and manage per local institutional standards.

Patients who experience >480 msec QTcF prolongation and undergo dose interruption and/or reduction must be monitored closely with ECGs, performed twice weekly for the first week of the QTcF prolongation and then weekly thereafter until the QTcF prolongation is resolved. If QTcF is > 450, evaluation of concomitant medications and electrolyte levels (including potassium and magnesium) are advised to assess for potential etiologies. Repeating ECGs daily for up to 3 days can occur to determine if the QTcF improves to allow administration of quizartinib.

8.3 Management of CPX-351-Related Adverse Events

Management for CPX-351-related AEs is located in Appendix G.

8.3.1 Criteria and Procedures for Dose Interruptions and Adjustments of CPX-351

If a patient develops non-hematologic Grade ≥3 AE(s) without resolution by 28 days from the first administration, or develop prolonged hematologic toxicities Grade ≥3 without count recovery 56 days or longer from first administration, the AEs will be considered severe AEs. However, this will not remove the patient from staying on study to receive quizartinib unless the PI believes quizartinib will exacerbate or prolong the toxicity.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

9.1 Complete Response (CR)

A CR will be defined as no morphologic, immunohistochemical, or flow cytometric evidence of disease by BM biopsy/aspirate and a peripheral CBC with platelet count ≥100,000/μL and ANC ≥1000/uL at the time of the bone marrow biopsy/aspirate. A molecular CR (CRm) is defined as having no evidence of disease by BM biopsy/aspirate by morphology, immunohistochemistry, flow cytometry, and FLT3 mutation by MRD analysis. Patients with a CR but with residual MRD positivity (CR MRD^{+}) are classified as indicated.

9.2 Complete Response with Incomplete Hematologic Recovery (CRi)

A CR with incomplete hematologic recovery (CRi) is defined as no morphologic, immunohistochemical, or flow cytometric evidence of disease by BM biopsy/aspirate, but with a persistent platelet count <100,000/µL and/or ANC <1000/µL at the time of BM biopsy/aspirate.

9.3 Partial Response (PR)

A PR is an incomplete response to treatment, defined as having persistent disease by morphology, but a >50% reduction in the blast count/cellularity ratio compared to the most recent BM biopsy prior to treatment.

9.4 Treatment Failure

Treatment failure is defined as patients who have achieved less than a PR at the time of response assessment.

9.5 Duration of Response (DOR)

Duration of response is defined as the number of days from the time of the first BM biopsy/aspirate where CR or CRi is identified to relapse. Patients who demonstrate no evidence of disease and no relapse while on study or who died for reasons other than disease relapse will be censored at the date of the last disease assessment..

9.6 Time-to-Progression (TTP)

Time-to-progression is defined as the number of days between diagnosis of relapse or refractory AML to disease progression, confirmed by bone marrow biopsy.

9.7 Event-free Survival (EFS)

Event-free survival is calculated as the number of days from the first date of treatment to the first date of evidence of PD by BM biopsy/aspirate, or death, regardless of cause. Patients who are alive without a disease response assessment of relapsed disease will be censored at the last adequate disease assessment date. Patients without a disease response assessment will be censored at the first date of treatment. This calculation does not pertain to Long Term Follow-up data.

9.8 Recurrence of Disease

Recurrent malignancy will be defined by hematologic criteria. Recurrent malignancy will also be defined as any unplanned medical intervention designed to prevent progression of malignant disease in patients who have molecular, cytogenetic, or flow cytometric evidence of malignant cells after transplantation.

9.9 Overall Survival (OS)

Overall survival is defined as the time from the first date of treatment until death as a result of any cause. For OS time, patients that have not died or are lost to follow-up will be censored at the date the patient was last known to be alive or the date of last contact.

9.10 Time to Absolute Neutrophil Count (ANC) and Platelet Count Recovery

Time to neutrophil recovery is defined as the time from each CPX-351 cycle Day 1 to when the peripheral ANC is ≥500/μL. Time to platelet recovery is defined as the time from each CPX-351 cycle to when the peripheral blood platelet count is >50,000/ μL. Delayed neutrophil recovery is defined as having an ANC <500/μL >56 days from each CPX-351 cycle Day 1. Delayed platelet recovery is defined as having a platelet count <50,000 >56 days from each CPX-351 cycle Day 1.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This is a multi-center, open-label, two-part prospective Phase II study of patients with relapsed or refractory FLT3-ITD mutation-positive AML. The study is designed to assess the safety and tolerability as well as the efficacy of administering CPX-351 with quizartinib, a second-generation FLT3 inhibitor.

A response rate (CR + CRi) of ≥50% is targeted with 40% or less considered unacceptable. This is assumed to be an acceptable estimate based on CR + CRi/CRp of 48.2% reported with quizartinib monotherapy in a relapsed or refractory patient with FLT3-ITD AML (Cortes et al 2019). Of note, prior FLT3-targeting inhibitor exposure is permitted on this study. However, patients receiving a prior FLT3-targeting inhibitor were excluded in the QUANTUM-R study. Expected CR+CRi in relapsed or refractory patients receiving standard intensive or non-intensive salvage chemotherapy harboring an FLT3 mutation is 27% (Cortes et al 2019). The estimated response in those with relapsed/refractory FLT3-ITD AML receiving CPX-351 alone cannot be estimated. However, in a poor-risk EPI patient population, CR+CRi was reported as 39.3% (Cortes et al 2015). However, FLT3-ITD mutation presence was not utilized in the generation of EPI prognostication, and those with an FLT3-ITD mutation could in fact have a reduced response within all EPI risk groups. Thus, the expected response must be based upon the QUANTUM-R study of those receiving standard salvage options harboring an FLT3-ITD mutation.

In the safety lead-in, 10 patients will be enrolled to receive CPX-351 with quizartinib. If >3 patients experience delayed neutrophil count recovery >56 days or delayed thrombocytopenia recovery >56 days from the first day on the study regimen, or if >3 patients develop a non-hematologic toxicity, defined as a Grade 4 non-hematologic AE determined to be probably related to the combined treatment or a Grade 4 neutropenia, then the study will be terminated.

Assuming safety parameters are met, the first 10 patients will be followed for response in Part 2 of the study.

10.2 Sample Size Considerations

The null hypothesis that the ORR (defined as CR + CRi) is ≤27% (Cortes et al 2019) will be tested against a one-sided exact alternative ORR of 50% at a target significance level of 0.05. A sample size of 30 evaluable patients achieves 80% power if the true ORR is ≥50%. The null

hypothesis will be rejected if 13 or more responses are observed in 30 evaluable patients. In order to allow for a non-evaluable rate of 10%, a total of 34 patients will be enrolled in the study.

10.3 Analysis Population

The following analysis populations will be used:

- The Safety Analysis Set is defined as all patients who received at least one dose of CPX-351 or quizartinib.
- The Efficacy Analysis Set is defined as all patients who received at least one dose of CPX-351 or quizartinib, who have an adequate baseline disease assessment, and an adequate post-baseline assessment and who discontinue due to death or PD prior to their first assessment.

10.4 Data Analysis

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

10.4.1 Demographics and Baseline Characteristics

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

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

10.4.2 Efficacy Analysis

All efficacy analyses will be performed using the Efficacy Analysis Set.

The ORR is defined as the proportion of patients achieving a response of CR or CRi at the time of the recovery assessment. For ORR, point estimates and the associated 95% CIs (based on the Clopper-Pearson method) will be calculated.

For DOR, the estimate of the median based on Kaplan-Meier analyses will be reported. For EFS and OS, the estimated rates at 6, 12, and 24 months based on Kaplan-Meier analyses will be reported.

10.4.3 Safety Analysis

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy, and will be graded according to NCI CTCAE Version 5.0. A copy of the CTCAE scoring system may be downloaded from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

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

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

Concomitant medications will be coded using the WHO-Drug Dictionary, and they will be listed and summarized.

10.5 Analysis Time Points

10.5.1 Safety Review

The safety lead-in consists of the first 10 patients enrolled. If >3 patients experience delayed neutrophil count recovery >56 days from the first day receiving the study regimen, defined as having a peripheral blood ANC <500/µL without evidence of residual disease by BM biopsy, or if >3 patients develop a non-hematologic toxicity, defined as a Grade 4 non-hematologic AE determined to be probably related to the combined treatment, then the study will be terminated.

10.5.2 Final Analysis

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

11. SAFETY REPORTING AND ANALYSES

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

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

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

11.1 Definitions

11.1.1 Adverse Events

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

AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose (including overdose).

11.1.2 Serious Adverse Events

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

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

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

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

11.1.3 Adverse Reaction

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

11.1.4 Suspected Adverse Reaction

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

11.1.5 Recording and Reporting of Adverse Events

11.1.5.1 Recording of Adverse Events

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

A description of the event, including its date of onset and resolution, whether it constitutes an SAE or not, any action taken (e.g., changes to study treatment), and outcome should be provided along with the Investigator's assessment of causality (e.g., the relationship to the study treatment). For an AE to be a suspected TEAE, there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE Version 5.0, and changes will be documented.

If the AE is serious, it should be reported immediately to the Development Innovations Safety Department. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (e.g., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

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

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

11.1.5.2 Reporting Period for Adverse Events

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

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

After 100 days after completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the Investigator as treatment-related are to be reported.

11.1.6 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (e.g., start

and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

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

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

11.2 Serious Adverse Event Reporting by Investigators

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

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

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

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

Development Innovations Safety Department

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

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

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

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the Development Innovations Safety Department as soon as it is available; these reports should be submitted using the Development Innovations SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual.

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

11.3 Recording of Adverse Events and Serious Adverse Events

11.3.1 Diagnosis versus Signs and Symptoms

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

Progression of malignancy (including fatal outcomes), if documented by use of an appropriate method (for example, as per Response Evaluation Criteria in Solid Tumors [RECIST] criteria for solid tumors), should not be reported as an SAE.

11.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF screen.

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

11.3.3 Abnormal Laboratory Values

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

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

11.3.4 Deaths

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

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

11.3.5 Hospitalization, Prolonged Hospitalization, or Surgery

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

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

- Emergency department or emergency room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, custodial care or respite care facility

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

11.3.6 Pre-Existing Medical Conditions

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

11.3.7 New Cancers

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

11.3.8 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

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

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

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

11.3.9 Overdose

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

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

11.4 Protocol-Defined Adverse Events of Special Interest (AESI)

The following are adverse events of special interest (AESIs), and will need to be reported expeditiously (see Section 11.1.5).

11.4.1.1 QTc Prolongation, TdP and Other Ventricular Arrhythmias

Subjects who experience >480 msec QTcF prolongation and undergo dose interruption and/or reduction must be monitored closely with ECGs, performed twice weekly for the first week of the QTcF prolongation and then weekly thereafter until the QTcF prolongation is resolved, as described in Section 8.2.1. A Grade ≥3 QTcF prolongation either serious or non-serious and whether or not causally related, must be recorded as AE or SAE in the Electronic Data Capture (EDC) system within 24 hours of awareness of the central ECG laboratory reading, with the Investigator's assessment of seriousness, causality, and a detailed narrative.

11.4.1.2 Combined Elevations of Aminotransferases and Bilirubin

Combined elevations of aminotransferases and bilirubin, either serious or non-serious and whether or not causally related, meeting the laboratory criteria of a potential Hy's Law case [ALT or AST ≥3 x ULN with simultaneous total bilirubin ≥2 x ULN] should always be recorded as an AE or SAE within 24 hours of awareness, with the Investigator's assessment of

seriousness, causality, and a detailed narrative. Patients will be monitored as described in Appendix F.

11.5 Funding Partner Serious Adverse Event Reporting Requirements

The Development Innovations Safety Department will forward SAE, AESI, non-serious AESI, and overdose information regarding CPX-351 to Jazz Pharmaceuticals at AEreporting@jazzpharma.com and quizartinib to Daiichi Sankyo Clinical Safety and Pharmacovigilance (CSPV) at CSPV-Clinical@dsi.com or Daiichi Sankyo fax (732) 906-9621 within 1 business day of the Development Innovations Safety Department personnel becoming aware of the SAE.

Development Innovations is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with International Council for Harmonisation (ICH) guidelines and US Food and Drug Administration (FDA) regulations.

11.5.1 Sponsor Assessment of Unexpected Events

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

An AE or SAR is considered "unexpected" when the following conditions occur:

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

When applicable, an unexpected AE may also apply to an event that is not listed in the current USPI or an event that may be mentioned in the USPI, but differs from the event because of greater severity or specificity.

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

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

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

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Study Monitoring, Auditing, and Inspecting

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

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

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

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

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

13.1 Institutional Review Board Approval

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

The PI/Sponsor and/or designee will follow all necessary regulations to ensure appropriate initial and on-going IRB study review. The PI/Sponsor (as appropriate) must submit to and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF document. Investigators will be advised by the Study Chair/Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates will be prepared by Jazz Pharmaceuticals and Daiichi Sankyo or their representatives as required, for distribution to the Investigator(s) and submission to the relevant IRB.

13.2 Regulatory Approval

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

13.3 Informed Consent

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

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

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

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

13.3.1 Confidentiality

13.3.1.1 Patient Confidentiality

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

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

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

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

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

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

13.3.1.2 Investigator and Staff Information

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

13.4 Financial Information

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

14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

14.1 Amendments to the Protocol

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

If an amendment to the protocol is required, the amendment will be originated and documented by the Study Chair/Sponsor. All amendments require review and approval of the funding pharmaceutical company (Daiichi Sankyo and Jazz Pharmaceuticals) and the PI supporting the study. The written amendment must be reviewed and approved by the Study Chair/Sponsor and

Daiichi Sankyo and Jazz Pharmaceuticals, and submitted to the IRB at the Investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patients, increase to dosing or exposure, patient number increase, or the addition or removal of new tests or procedures shall be reviewed and approved by the IRB of record for the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable and IRB approval obtained, specifically when an increase to dosing or patient exposure and/or patient number has been proposed or when the addition or removal of an Investigator is necessitated.

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

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

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

14.2 Documentation Required to Initiate the Study

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

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

At a minimum the following documents required to begin a study in the US:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current curricula vitae for the PI and any associate Investigator(s) who will be involved in the study
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed

- A copy of the IRB-approved consent form containing permission for audit by representatives of Development Innovations, the IRB, and the FDA and other regulatory agencies (as applicable)
- Financial disclosure forms for all Investigators listed on Form FDA 1572 (if applicable)
- Site qualification reports, where applicable
- Verification of PI acceptability from local and/or national debarment list(s).

14.3 Study Documentation and Storage

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

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

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

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

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records, as per 21CFR Part 312.62, for a period of 2 years following the date

a marketing application is approved 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 indication, until 2 years after the investigation is discontinued and FDA has been notified of the discontinuation.

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

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

14.4 Data Collection

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

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

All data requested in the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for the change should be provided. The Investigator will electronically sign and date the patient eCRF casebook, indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the PI, once all data for that patient is final.

14.5 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. Jazz Pharmaceuticals and

Daiichi Sankyo reserve the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication process.

Inclusion of the Investigator in the authorship of any multicenter publication will be based upon substantial contribution to the design, analysis, and interpretation of data, and the drafting and/or critically revising any manuscript(s) derived from the study. The Investigator acknowledges that the site is part of a multicenter study and agrees that any publication by the Investigator of the results of the study conducted at his/her research site shall not be made before the first multicenter publication.

In the event there is no multicenter publication within 15 months after the study has been completed or terminated at all study sites, and all data has been received, the Investigator shall have the right to publish his/her results from the study, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the Investigator shall withhold any publication or presentation an additional 60 days solely to permit the Sponsor to seek patent protection and to remove any Development Innovations confidential information from all publications.

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16. APPENDICES

Appendix A: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death 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: New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

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

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

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

Acceptable Contraception Methods:

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly-effective contraception during the study and until 6 months following the last dose of CPX-351 and/or quizartinib.

Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential, must use condoms plus a spermicidal agent during the study treatment period and for 6 months following their last dose of CPX-351 and/or quizartinib, and must not father a child during this period.

Male patients must also refrain from donating sperm during their participation in the study for 6 months following their last dose of CPX-351 and/or quizartinib.

Highly effective contraception is defined as either:

True Abstinence	When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
Sterilization	When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
Male Partner Sterilization	With the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.

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

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

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

The following are acceptable forms of barrier contraception:

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

Unacceptable Contraception Methods: for women of childbearing potential include:

- IUD progesterone T

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

Pregnancies

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

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

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

Women Not of Childbearing Potential are Defined as Follows:

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

Appendix D: Schedule of Assessments

ASSESSMENTS	Screening	Induction/Re-induction[a]								Consolidation[b]						At ~D30 interim[c]	Maintenance[d]		EOT	F/U
Day		D1	D3	D5	D6[n]	D8	D14	D21	D35	D1	D3	D6	D14	D21	D35		D1	D15		
Informed consent[e]	X																			
Inclusion/exclusion criteria	X																			
Medical history and demographics	X[f]																			
Physical examination, height (screening only), and weight[g]	X[f]		X	X	X[n]	X	X	X	X	X	X	X			X	X	X	X	X	
Vital signs[h]	X[f]		X	X	X[n]	X	X	X	X	X	X	X			X	X	X	X	X	
ECOG performance status	X[f]		X	X	X[n]	X	X	X	X	X	X	X			X	X	X	X	X	
12-lead electrocardiogram[f]	X[f]				X[n]	X	X	X			X	X	X	X			X	X	X	
TTE or MUGA scan	X[f]																			
Adverse event monitoring		X	X	X	X[n]	X	X	X	X	X	X	X			X	X	X	X	X	
Concomitant medication review	X	X	X	X	X[n]	X	X	X	X	X	X	X			X	X	X	X	X	
Lumbar puncture[i]		X																		

ASSESSMENTS	Screening	Induction/Re-induction[a]								Consolidation[b]						At ~D30 interim[c]	Maintenance[d]		EOT	F/U
Day		D1	D3	D5	D6[n]	D8	D14	D21	D35	D1	D3	D6	D14	D21	D35		D1	D15		
Central line placement (PICC or port)	Per institutional standards; placed prior to starting study treatment																			
CPX-351		Once daily (IV) on Days 1, 3 & 5. If re-induction is necessary administer on Days 1 & 3. During consolidation, administer on Days 1 & 3 for 2 cycles.																		
Quizartinib		Once daily (PO) Days 8-21 with induction. Days 6-21 with re-induction and/or consolidation(s).															Days 1-28 until PD			
Hematology panel	X[f]	X	X	X	X[n]	X	X	X	X	X	X	X			X	X	X	X	X	
Clinical chemistry panel	X[f]	X	X	X	X[n]	X	X	X	X	X	X	X			X	X	X	X	X	
Virus testing	X[f]																			
Urinalysis	X[f]																			
Serum Pregnancy Test[f,j]	X	X								X							Every 3 Cycles			
Bone marrow aspirate and biopsy (includes FLT3 mutation test via PCR)[k]	X							X	X						X	X[k]	Day 24 (± 3) at cycles 3, 6, 12 and 24			

ASSESSMENTS	Screening	Induction/Re-induction[a]								Consolidation[b]						At ~D30 interim[c]	Maintenance[d]		EOT	F/U
Day		D1	D3	D5	D6[n]	D8	D14	D21	D35	D1	D3	D6	D14	D21	D35		D1	D15		
MRD analysis (FLT3 via NGS)[l]									X						X	X[l]	Day 24 (± 3) at cycles 3, 6, 12 and 24			
Underlying disease assessment	X																			X[m]
Survival status																				X[m]

a **Induction:** CPX-351 (daunorubicin 44 mg/m^2 IV and cytarabine 100 mg/m^2 IV) will be given IV on Days 1, 3, and 5 during induction therapy followed by quizartinib 30 mg orally (PO) once daily on Days 8-21 (hold quizartinib on Day 21). Patients with an incomplete response, but a >50% reduction in the blast count/cellularity ratio compared to the most recent BM biopsy prior to treatment, may receive one additional cycle of induction therapy (re-induction) with CPX-351 (daunorubicin 44 mg/m^2 IV and cytarabine 100 mg/m^2 IV) on Days 1 and 3 (see Section 5.2.2). During **re-induction**, begin CPX-351 at least 72 hours after the last dose of quizartinib. Treatment with quizartinib will resume on Day 6 and continue through Day 21 (hold quizartinib on Day 21, if proceeding to consolidation phase) (see Section 5.2.3).

b **Consolidation:** Patients who achieve CR and do not proceed to an alloHCT or other CT intervention will proceed to the consolidation phase beginning 7 days (± 7 days) after neutrophil recovery (ANC >1000/µL). Administer up to 2 consolidation cycles of CPX-351 (daunorubicin 29 mg/m^2 IV and cytarabine 65 mg/m^2 IV) on Days 1 and 3. Begin quizartinib 30 mg PO once daily on Days 6-21 (hold quizartinib on Day 21) (see Section 5.2.3). Administration cannot begin earlier than 24 hours from the last administration of CPX-351 (see Section 7.2).

c **The 60-day period (~Day 30) between the end of consolidation and the start of maintenance therapy.** Patients who proceed to alloHCT or other CT intervention after consolidation will resume quizartinib maintenance 30-60 days from the intervention. In patients who proceed to alloHCT, begin quizartinib maintenance no earlier than day 30 after transplant (see Section 5.2.4).

d **Maintenance:** Maintenance dosing of quizartinib will begin at 30 mg/day on Days 1-14, and if there are no toxicities and QTcF is maintained ≤450 msec, will increase to 60 mg/day on Day 15. The maintenance phase is a 28-day cycle beginning 7 days (± 7 days) after neutrophil recovery from the consolidation phase or induction phase. Patients will receive quizartinib once daily for a total of 24 cycles or until disease relapse. Patients who proceed to alloHCT or other CT intervention **after** consolidation will resume quizartinib maintenance 30-60 days from the intervention for a total of 24 cycles or until disease relapse. If the patient is on quizartinib prior to HCT or CT intervention, quizartinib should be discontinued 7 days prior if a conditioning therapy is utilized. If ≥2 CT interventions (e.g., repeat DLI) are planned after maintenance, a 28-day hold is acceptable, with resumption of quizartinib with the next cycle (see Section 5.2.4).

e Informed consent must be obtained prior to the initiation of any screening test or procedure.

f The screening medical history, physical examination, vital signs, ECOG performance status, and triplicate ECGs, TTE/MUGA, baseline signs and symptoms and safety laboratory tests (including pregnancy and virus testing [hepatitis serology (Hepatitis B surface antigen and antibody and Hepatitis C antibody), HIV-1, 2]) should be done following written consent and prior to initiation of therapy.

g Physical examination will include measurements of height (screening only) and weight.

h Vital signs will include resting heart rate, blood pressure, respiratory rate, and temperature.

i Patients will receive a lumbar puncture during pre-transplant workup, per institutional practices and following site-specific standard operating procedures within the first 2 weeks on study treatment. No further intrathecal (IT) chemotherapy is required in this study if there is no evidence of disease. In patients who have CNS disease involvement, IT chemotherapy should continue every 4 days (±1 day) until disease clearance, followed by every 7 days (±2 days) for 2 additional administrations. Thereafter, administer IT chemotherapy every 28 days (± 7 days) for at least 12 cycles (see Section 6.3).

j A serum beta human chorionic gonadotropin pregnancy test must be done 72 hours prior to the start of treatment for women of child-bearing potential. Serum Pregnancy tests are also required prior to the start of each cycle during the induction and consolidation phases, during maintenance phase a serum pregnancy test will obtained once every 3 cycles.

k BM biopsies and aspirates will be collected at screening, Day 21 (±7 days) during induction, and Day 35 (±7 days) during both induction and consolidation phases (the time of count recovery after CPX-351 + quizartinib, defined as obtaining a BM biopsy within 4 days of having an ANC >500 for ≥24 hours) and at Day 28 (+/-7 days) post-alloHCT or other CT intervention (if applicable). In the maintenance phase, BM biopsies and aspirates will also be collected on Day 24 (±3 days) during cycles 3, 6, 12, and 24. Thereafter, assessment of disease status will be at the discretion of the haematologist/oncologist. All biopsies should include monitoring for FLT3 mutation by PCR (see Section 6.5.11).

l MRD analyses with BM and aspirates and blood samples: Collect samples during BM recovery at the end of induction and consolidation phases (Cycle 1 Day 35 (±7 days) and Cycle 2 Day 35 (±7 days), 30 days post-alloHCT or other CT intervention (if applicable), and during the maintenance phase at Day 24 (±3 days) Cycles 3, 6, 12, and 24.

m Patients will be followed every 6 months during the 2 years after discontinuing study treatment for an underlying disease assessment (performed per Appendix E) and survival.

n Cycle 2 of induction only.

Appendix E ASBMT RFI 2017 – Disease Classifications Corresponding to CIBMTR Classifications

ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^

AML and ALL
precursor B-lymphoblastic lymphoma/leukemia {per W.H.O. reclassified from lymphoma}
precursor T-lymphoblastic lymphoma/leukemia
	Low risk:
	CR 1
		First complete remission (CR1): A treatment response where all of the following criteria are met for at least four weeks*†:
		• Hematological: no blast cells in the peripheral blood, < 5% blasts in the bone marrow, no blasts with Auer rods (AML only), normal maturation of all cellular components in the marrow, normal CBC and ANC of > 1,000/µL
		• Platelets ≥ 100,000/µL*†
		• Transfusion independent
		• No other signs or symptoms of disease, including extramedullary disease(e.g., central nervous system or soft tissue involvement)
		  • Include recipients with persistent cytogenetic abnormality who otherwise meet all the criteria of CR. CIBMTR collects information about cytogenetic and molecular testing for those in CR (hematologic CR), however these are only relevant for RFI reporting in as much as the centers judge importance of residual cytogenetic abnormalities in determining current status beyond the hematic criteria.
		  • *In some cases, there may not be a four-week interval between the completion of treatment for disease and the disease assessment immediately prior to the HSCT. If this is the case, CR should still be reported as the status at transplantation. Although this is an exception to the general condition that CR is "durable" beyond four weeks, the status of CR represents the "best assessment" prior to HSCT. Similarly, sufficient time may not have elapsed to allow for platelet recovery to normal levels and physician judgment is required to interpret whether residual low platelet counts may reflect residual disease.
		
		NOTE: Recipients with MDS that transformed to AML
		If the recipient has residual MDS following treatment for AML, report the AML disease status as either PIF or relapse (i.e., the recipient cannot be in an AML CR if there is evidence of MDS at the time of assessment).

AML and ALL (con"t)	Intermediate risk: CR2, CR3+	**Complete remission 2nd or greater (CR2/+)†:** Recipient achieved CR as defined above, relapsed and achieved CR again. Final pre-HSCT status must be CR.
AML and ALL (con"t)	High risk (not in remission):	**Never treated**: The recipient was diagnosed with acute leukemia and never treated. For example, this disease status may be appropriate if MDS was initially diagnosed and

ASBMT Diagnosis Category	ASBMT RFI Classification	CIBMTR Classification^
	Never treated Primary Induction Failure (PIF) Relapse	treated, the MDS then transformed into AML, and a decision was made to proceed immediately to transplant instead of treating the AML with therapy. **Primary Induction Failure (PIF):** The recipient was treated for acute leukemia but **never achieved** durable* **complete remission** with any therapy (*including relapsed < 1 mo from CR1 determination). The term **"**PIF" is not limited to the number of treatments used unsuccessfully. **Relapse:** Recurrence of disease after CR. Relapse is defined as: • ≥ 5% blasts in the marrow • Extramedullary disease • Reappearance of cytogenetic abnormalities and/or molecular markers associated with the diagnosis that, in the judgement of a physician, are at a level representing relapse. • Although CIBMTR collects information upon the number of the relapse, this information is not needed for the ASBMT RFI

Source: https://higherlogicdownload.s3.amazonaws.com/ASBMT/43a1f41f-55cb-4c97-9e78-c03e867db505/UploadedImages/ASBMT_RFI_2018B_CIBMTR_Disease_Classifications.pdf

Appendix F Management of Quizartinib-Associated Adverse Events

QTcF (QT interval corrected with Fridericia's formula) Prolongation

- Grade 1
    - Check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTc interval. Continue quizartinib at the same dose.
- Grade 2 (QTcF average of triplicate readings >480 msec)
    - Check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTc interval.
    - The dose will be reduced without interruption (See Table 2). Following dose reduction, the quizartinib/placebo dose may be resumed at the previous level in the next cycle if the QTcF has decreased to within 30 msec of baseline or <450 msec but subject must be monitored closely for QT prolongation for the first cycle at the increased dose.
    - If 20 mg/day is the current dose, dosing will be interrupted for up to 14 days. If QTcF returns to within 30 msec of baseline or ≤450 msec within 14 days, treatment may be resumed at 20 mg/day.
- Grade 3 (QTcF average of triplicate readings >500 msec)
    - Check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTc interval.
    - Dosing will be interrupted for up to 14 days. If QTcF returns to within 30 msec of baseline or ≤450 msec within 14 days, treatment may be resumed at a reduced dose (See Table 2).
    - If 20 mg/day is the current dose, dosing will be interrupted for up to 14 days. If QTcF returns to within 30 msec of baseline or ≤450 msec within 14 days, treatment may be resumed at 20 mg/day. If Grade 3 event returns, treatment will be discontinued.
- Grade 4 (QTcF >500 msec or >60 msec change from baseline, and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)
    - Treatment will be permanently discontinued.

Differentiation Syndrome

- Patients with suspected differentiation syndrome should promptly start treatment with systemic glucocorticoids and hemodynamic monitoring per local principal investigator or institutional preference until improvement. Treatment should be held until resolution to < Grade 3.

Non-Hematologic Toxicity

Grade 3 or 4 non-hematologic toxicity that is at least possibly related to quizartinib and persisting >48 hours without improvement to ≤ Grade 2 or without waiting 48 hours if in the Investigators judgment the AE poses a serious risk to the patient:

- Dosing will be interrupted for up to 28 days.
    - If toxicity improves to Grade ≤1 within 28 days, treatment may be resumed at the previous dose.
    - If toxicity improves to Grade ≤2 within 28 days, treatment may be resumed at a reduced dose (1 level) (See Table 2).
    - If toxicity does not improve/resolve within 28 days, then quizartinib will be discontinued.

Hepatic Events and Liver Enzyme Elevation

Elevation of liver enzymes that meet the criteria below should be investigated and the cause identified when possible:

- ALT >8 × ULN; or
- AST or ALT >5 x ULN for more than two weeks; or
- ALT or AST >3 x ULN, but not reaching the limits in the above criteria, in combination with clinical symptoms suggestive of hepatitis; or
- ALT or AST >3 x ULN with TBL >2 x ULN*
    - Combined elevations of ALT or AST with TBL as described above will be treated as Adverse Events of Special Interest and reported as per Section 11.2.*

Once the cause of liver enzyme elevation is identified, remove or treat the contributing cause. If the above criteria are met and the elevation is considered to be related or possibly related to quizartinib, then quizartinib dosing should be interrupted.

Liver enzyme level testing will be repeated at least weekly, or more frequently, based on degree of hepatic laboratory abnormality. If the liver enzyme levels return to baseline levels, quizartinib may be resumed at the full dose. If toxicity does not improve/resolve within 28 days, then quizartinib will be discontinued.

Upon resumption of quizartinib, if liver enzyme elevations recur, treatment may be resumed at a reduced dose following return to baseline levels.

Liver Safety Monitoring and Evaluations

Any patient who temporarily interrupts or permanently discontinues quizartinib due to confirmed liver enzyme abnormalities and/or jaundice in the absence of a known cause, must have an evaluation to determine the cause of the event.

Evaluation may include the following depending on the clinical situation:

- Medical history and physical exam, including focus on medications and substances used: alcohol, acetaminophen, azole antifungals, change in medication dosages, new

medications added, over the counter medication use and recreational drug use. Check for change in diet or use of dietary supplements

- Abdominal ultrasound
- Hepatitis B, and C screening (hepatitis B surface antigen, and anti-hepatitis C virus plus viral titer), antinuclear antibody and anti-Smith antibody, cytomegalovirus, Epstein Barr virus
- Additional evaluations as deemed appropriate by the Investigator to exclude other causes of liver enzyme and bilirubin elevations
- All laboratory results, including local laboratory reference ranges are to be recorded.

Myelosuppression (Maintenance Phase)

Quizartinib should be reduced or dosing interrupted (See Table 3) at the Investigator's discretion if:

- The patient has been treated for a minimum of 2 cycles;
- Platelet count is <100,000/mm3 and ANC ≤1000/mm3; and
- There is no evidence of relapse.

The dose of quizartinib may be reduced stepwise from 60 mg/day to 30 mg/day to 20 mg/day. For patients experiencing myelosuppression requiring dose reduction while taking a dose of 30 mg/day (20 mg/day in patients receiving a strong CYP3A4inhibitor), dosing will be interrupted.

Appendix G Management of CPX-351-Related Adverse Events

NCI CTCAE Grade	CPX-351 Action
Cardiotoxicity	Discontinue **CPX-351** immediately without resumption
Hypersensitivity Grade 1	Once symptoms resolve, reinitiate infusion at half the prior rate of infusion. Consider premedication with antihistamines and/or corticosteroids for subsequent doses.
Hypersensitivity Grade 2	Do not reinitiate infusion. For subsequent doses, pre-medicate with antihistamines and/or corticosteroids prior to initiating infusion at same rate.
Hypersensitivity Grade ¾	Permanently discontinue treatment, treat according to the standard of care to manage symptoms, and monitor patient until symptoms resolve.
Neutropenia lasting ≥56 days	**Proceed to maintenance therapy with quizartinib**
Thrombocytopenia lasting ≥56 days	**Proceed to maintenance therapy with quizartinib**

Appendix H Cytochrome P450 3A4 Inhibitors and Inducers

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

CYP3A4 Inhibitors	CYP3A4 Inducers
Strong Inhibitors	Barbiturates
Clarithromycin	Carbamazepine
Indinavir	Efavirenz
Itraconazole	Glucocorticoids
Ketoconazole	Modafinil
Nefazodone	Nevirapine
Posaconazole	Oxcarbazepine
Ritonavir	Phenobarbital
Saquinavir	Phenytoin
Suboxone	Pioglitazone
Telithromycin	Rifabutin
Voriconazole	St. John's Wort
Intermediate Strength Inhibitors	Troglitazone
Aprepitant	
Erythromycin	
Fluconazole	
Isavuconazole	
Verapamil	
Diltiazem	
Weak Inhibitors	
cimetidine	
Other Possible Inhibitors	
Amiodarone	
Boceprevir	
Chloramphenicol	
Ciprofloxacin	
Delaviridine	
Diethyl-dithiocarbamate	
Fluvoxamine	
Gestodene	
Imatinib	
Mibefradil	
Mifepristone	
Norfloxacin	
Norfluoxetine	
Starfruit	
Telaprevir	

Appendix I Drugs That Prolong QT Interval and/or Induce Torsades De Pointes

Drugs with known or possible risk of QT prolongation and/or Torsades de pointes should be avoided for all patients from screening through permanent discontinuation of study treatment. Please note that the list below was derived from www.crediblemeds.org on 07 October 2019 and serves only as guidance. Since CredibleMeds® constantly assesses new drug information and updates its lists, sites should go directly to the crediblemeds.org website in real-time for reference.

COMBINED LIST OF DRUGS THAT PROLONG QT AND/OR CAUSE TORSADES DE POINTES (TDP)

CredibleMeds® has reviewed available evidence for the drugs on the following list and place them in one of three designated categories: Known Risk of TdP (KR), Possible Risk of TdP (PR) or have a Conditional Risk of TdP (CR). The full description of these categories can be found on the CredibleMeds.org website.

Generic Name	Brand Name
Abarelix (PR)	Plenaxis
Abiraterone (CR)	Zytiga and others
Aclarubicin (KR)	Aclacin and others
Alfuzosin (PR)	Uroxatral
Alimemazine (Trimeprazine) (PR)	Nedeltran and others
Amantadine (CR)	Symmetrel and others
Amiodarone (KR)	Cordarone and others
Amisulpride (CR)	Solian and others
Amitriptyline (CR)	Elavil (Discontinued 6/13) and others
Amphotericin B (CR)	Fungilin and others
Amsacrine (Acridinyl anisidide) (CR)	Amsidine
Anagrelide (KR)	Agrylin and others
Apalutamide (PR)	Erleada
Apomorphine (PR)	Apokyn and others
Aripiprazole (PR)	Abilify and others
Arsenic trioxide (KR)	Trisenox
Artemether/Lumefantrine (PR)	Coartem
Artenimol/piperaquine (PR)	Eurartesim
Asenapine (PR)	Saphris and others
Astemizole (KR)	Hismanal
Atazanavir (CR)	Reyataz and others
Atomoxetine (PR)	Strattera

Generic Name	Brand Name
Azithromycin (KR)	Zithromax and others
Bedaquiline (PR)	Sirturo
Bendamustine (PR)	Treanda and others
Bendroflumethiazide (Bendrofluazide) (CR)	Aprinox and others
Benperidol (PR)	Anquil and others
Bepridil (KR)	Vascor
Betrixaban (PR)	Bevyxxa
Bortezomib (PR)	Velcade and others
Bosutinib (PR)	Bosulif
Buprenorphine (PR)	Butrans and others
Cabozantinib (PR)	Cometriq
Capecitabine (PR)	Xeloda
Ceritinib (PR)	Zykadia
Chloral hydrate (CR)	Aquachloral and others
Chloroquine (KR)	Aralen
Chlorpromazine (KR)	Thorazine and others
Cilostazol (KR)	Pletal
Cimetidine (CR)	Tagamet and others
Ciprofloxacin (KR)	Cipro and others
Cisapride (KR)	Propulsid
Citalopram (KR)	Celexa and others
Clarithromycin (KR)	Biaxin and others

Generic Name	Brand Name
Clofazimine (PR)	Lamprene
Clomipramine (PR)	Anafranil
Clotiapine (PR)	Entumine
Clozapine (PR)	Clozaril and others
Cobimetinib (PR)	Cotellic
Cocaine (KR)	Cocaine
Crizotinib (PR)	Xalkori
Cyamemazine (Cyamepromazine) (PR)	Tercian
Dabrafenib (PR)	Tafinlar
Dasatinib (PR)	Sprycel
Degarelix (PR)	Firmagon and others
Delamanid (PR)	Deltyba
Desipramine (PR)	Pertofrane and others
Deutetrabenazine (PR)	Austedo
Dexmedetomidine (PR)	Precedex and others
Dextromethorphan/Quinidine (PR)	Nuedexta
Diphenhydramine (CR)	Benadryl and others
Disopyramide (KR)	Norpace
Dofetilide (KR)	Tikosyn
Dolasetron (PR)	Anzemet
Domperidone (KR)	Motilium and others
Donepezil (KR)	Aricept

Generic Name	Brand Name
Nilotinib (PR)	Tasigna
Norfloxacin (PR)	Noroxin and others
Nortriptyline (PR)	Pamelor and others
Nusinersen (PR)	Spinraza
Ofloxacin (PR)	Floxin
Olanzapine (CR)	Zyprexa and others
Omeprazole (CR)	Losec and others
Ondansetron (KR)	Zofran and others
Osimertinib (PR)	Tagrisso
Oxaliplatin (KR)	Eloxatin
Oxytocin (PR)	Pitocin and others
Paliperidone (PR)	Invega and others
Palonosetron (PR)	Aloxi
Panobinostat (PR)	Farydak
Pantoprazole (CR)	Protonix and others
Papaverine HCl (Intra-coronary) (KR)	none
Paroxetine (CR)	Paxil and others
Pasireotide (PR)	Signifor
Pazopanib (PR)	Votrient
Pentamidine (KR)	Pentam
Perflutren lipid microspheres (PR)	Definity and others
Perphenazine (PR)	Trilafon and others
Pilsicainide (PR)	Sunrythm
Pimavanserin (PR)	Nuplazid
Pimozide (KR)	Orap
Pipamperone (PR)	Dipiperon (E.U) and others
Piperacillin/Tazobactam (CR)	Tazosyn and Zosyn
Pitolisant (Tiprolisant) (PR)	Wakix
Posaconazole (CR)	Noxafil and others
Pretomanid (PR)	none

Generic Name	Brand Name
Primaquine phosphate (PR)	None found
Probucol (KR)	Lorelco
Procainamide (KR)	Pronestyl and others
Promethazine (PR)	Phenergan
Propafenone (CR)	Rythmol SR and others
Propofol (KR)	Diprivan and others
Prothipendyl (PR)	Dominal and others
Quetiapine (CR)	Seroquel
Quinidine (KR)	Quinaglute and others
Quinine sulfate (CR)	Qualaquin
Ranolazine (CR)	Ranexa and others
Ribociclib (PR)	Kisqali
Rilpivirine (PR)	Edurant and others
Risperidone (CR)	Risperdal
Romidepsin (PR)	Istodax
Roxithromycin (KR)	Rulide and others
Saquinavir (PR)	Invirase(combo)
Sertindole (PR)	Serdolect and others
Sertraline (CR)	Zoloft and others
Sevoflurane (KR)	Ultane and others
Siponimod (PR)	Mayzent
Solifenacin (CR)	Vesicare
Sorafenib (PR)	Nexavar
Sotalol (KR)	Betapace and others
Sparfloxacin (KR)	Zagam
Sulpiride (KR)	Dogmatil and others
Sultopride (KR)	Barnetil and others
Sunitinib (PR)	Sutent
Tacrolimus (PR)	Prograf and others

Generic Name	Brand Name
Tamoxifen (PR)	Nolvadex(discontinued 6/13) and others
Telaprevir (CR)	Incivo and others
Telavancin (PR)	Vibativ
Telithromycin (PR)	Ketek
Terfenadine (KR)	Seldane
Terlipressin (KR)	Teripress and others
Terodiline (KR)	Micturin and others
Tetrabenazine (PR)	Nitoman and others
Thioridazine (KR)	Mellaril and others
Tiapride (PR)	Tiapridal and others
Tipiracil/Trifluridine (PR)	Lonsurf
Tizanidine (PR)	Zanaflex and others
Tolterodine (PR)	Detrol and others
Toremifene (PR)	Fareston
Torsemide (Torasemide) (CR)	Demadex and others
Tramadol (PR)	Crispin and others
Trazodone (CR)	Desyrel (discontinued 6/13) and others
Trimipramine (PR)	Surmontil and others
Tropisetron (PR)	Navoban and others
Valbenazine (PR)	Ingrezza
Vandetanib (KR)	Caprelsa
Vardenafil (PR)	Levitra
Vemurafenib (PR)	Zelboraf
Venlafaxine (PR)	Effexor and others
Voriconazole (CR)	VFend
Vorinostat (PR)	Zolinza
Ziprasidone (CR)	Geodon and others
Zotepine (PR)	Losizopilon and others
Zuclopenthixol (Zuclopentixol) (PR)	Cisordinol and others

Note: Medicines on this list are reviewed on an ongoing basis to assure that the available evidence supports their continued placement on this list. Because, the list changes regularly, we recommend always checking the website at crediblemeds.org for the most up-to-date information. Most drugs have multiple brand names and it is not practical to list them on this form. The CredibleMeds.org website provides a partial list of the more common brands.

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Generated: October 7, 2019. List last revised: September 15, 2019

Generic Name	Brand Name
Doxepin (CR)	Sinequan and others
Dronedarone (KR)	Multaq
Droperidol (KR)	Inapsine and others
Efavirenz (PR)	Sustiva and others
Eliglustat (PR)	Cerdelga
Encorafenib (PR)	Braftovi
Entrectinib (PR)	Rozlytrek
Eperisone (CR)	Myonal and others
Epirubicin (PR)	Ellence and others
Eribulin mesylate (PR)	Halaven
Erythromycin (KR)	E.E.S. and others
Escitalopram (KR)	Cipralex and others
Esomeprazole (CR)	Nexium and others
Ezogabine (Retigabine) (PR)	Potiga and others
Famotidine (CR)	Pepcid and others
Felbamate (PR)	Felbatol
Fingolimod (PR)	Gilenya
Flecainide (KR)	Tambocor and others
Fluconazole (KR)	Diflucan and others
Fluorouracil (5-FU) (PR)	Adrucil and others
Fluoxetine (CR)	Prozac and others
Flupentixol (PR)	Depixol and others
Fluvoxamine (CR)	Faverin and others
Furosemide (frusemide) (CR)	Lasix and others
Galantamine (CR)	Reminyl and others
Garenoxacin (CR)	Geninax
Gatifloxacin (KR)	Tequin
Gemifloxacin (PR)	Factive

Generic Name	Brand Name
Gilteritinib (PR)	Xospata
Glasdegib (PR)	Daurismo
Granisetron (PR)	Kytril and others
Grepafloxacin (KR)	Raxar
Halofantrine (KR)	Halfan
Haloperidol (KR)	Haldol (US & UK) and others
Hydrochlorothiazide (CR)	Apo-Hydro and others
Hydrocodone - ER (PR)	Hysinglaå„¢ ER and others
Hydroquinidine (Dihydroquinidine) (KR)	Serecor
Hydroxychloroquine (CR)	Plaquenil and others
Hydroxyzine (CR)	Atarax and others
Ibogaine (KR)	None
Ibutilide (KR)	Corvert
Iloperidone (PR)	Fanapt and others
Imipramine (Melipramine) (PR)	Tofranil
Indapamide (CR)	Lozol and others
Inotuzumab ozogamicin (PR)	Besponsa
Isradipine (PR)	Dynacirc
Itraconazole (CR)	Sporanox and others
Ivabradine (CR)	Procoralan and others
Ivosidenib (PR)	Tibsovo
Ketanserin (PR)	Sufrexal
Ketoconazole (CR)	Nizoral and others
Lacidipine (PR)	Lacipil and others
Lansoprazole (CR)	Prevacid
Lapatinib (PR)	Tykerb and others
Lefamulin (PR)	Xenleta
Lenvatinib (PR)	Lenvima

Generic Name	Brand Name
Leuprolide (Leuprorelin) (PR)	Lupron and others
Levofloxacin (KR)	Levaquin and others
Levomepromazine (Methotrimeprazine) (KR)	Nosinan and others
Levomethadone (levamethadone) (PR)	
Levomethadyl acetate (KR)	Orlaam
Levosulpiride (KR)	Lesuride and others
Lithium (PR)	Eskalith and others
Lofexidine (PR)	Lucemyra
Loperamide (CR)	Imodium and many other OTC and Rx brands
Lopinavir/Ritonavir (PR)	Kaletra and others
Maprotiline (PR)	Ludiomil and others
Melperone (PR)	Bunil and others
Memantine (PR)	Namenda XR and many others
Mesoridazine (KR)	Serentil
Methadone (KR)	Dolophine and others
Metoclopramide (CR)	Reglan and others
Metolazone (CR)	Zytanix and others
Metronidazole (CR)	Flagyl and many others
Mianserin (PR)	Tolvon
Midostaurin (PR)	Rydapt
Mifepristone (PR)	Korlym and others
Mirabegron (PR)	Myrbetriq
Mirtazapine (PR)	Remeron
Moexipril/Hydrochlorothiazide (PR)	Uniretic and others
Moxifloxacin (KR)	Avelox and others
Necitumumab (PR)	Portrazza
Nelfinavir (CR)	Viracept
Nicardipine (PR)	Cardene