

**CLINICAL STUDY PROTOCOL**

<b>Protocol Number:</b>	<b>BSC-101-01</b>
<b>Protocol Title:</b>	A Phase 1/2a study of E6201 for the treatment of advanced hematologic malignancies with FLT3 and/or Ras mutations, including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML)
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<b>Amendment 3</b>	<b>August 26, 2015</b>
<b>Amendment 4</b>	<b>January 21, 2016</b>
<b>Amendment 5</b>	<b>May 5, 2016</b>
<b>Amendment 6</b>	<b>October 30, 2016</b>

**INVESTIGATOR SIGNATURE PAGE**

I have reviewed the above-titled protocol and agree that it contains all the information necessary to conduct the study as required. I will conduct the trial in accordance with the principles of the International Conference on Harmonisation (ICH) Good Clinical Practice, the Declaration of Helsinki and the applicable U.S. Food and Drug Administration (FDA) regulations.

I will maintain as confidential all written and verbal information provided to me by the Sponsor, including but not limited to, the protocol, case report forms, investigator's brochure, material supplied at investigator meetings, minutes of teleconferences, etc. Such material will only be provided as necessary to site personnel involved in the conduct of the trial, the Institutional Review Board (IRB) or local regulatory authorities.

I will obtain written informed consent from each prospective trial subject or each prospective trial subject's legal representative prior to conducting any protocol-specified procedures. The Informed Consent Document (ICD) used will have the approval of the IRB.

I will maintain adequate source documents and record all observations, treatments and procedures pertinent to trial subjects in their medical records. I will accurately complete and submit the electronic case report forms supplied by the Sponsor in a timely manner. I will ensure that my facilities and records will be available for inspection by representatives of Strategia Therapeutics, the IRB or local regulatory authorities. I will ensure that I and my staff are available to meet with representatives of Strategia Therapeutics during regularly-scheduled monitoring visits.

I will notify the Medical Monitor within 24 hours of any serious adverse events. Following this notification, a written report describing the serious adverse event will be provided to Strategia Therapeutics as soon as possible, but no later than 5 days following the initial notification.

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**Investigator's Signature**

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**Date**

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**Investigator's Name (Print)**

**SYNOPSIS**

<b>Sponsor</b> Strategia Therapeutics, Inc.	<b>Protocol Number</b> BSC-101-01
<b>Name of Study Drug</b> E6201 for Injection	<b>Protocol Title</b> A Phase 1/2a study of E6201 for the treatment of advanced hematologic malignancies with FLT3 and/or Ras mutations, including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML)
<b>Name of Active Ingredient</b> (3S,4R,5Z,8S,11E)-14-(Ethylamino)-8,9,16-trihydroxy-3,4-dimethyl-3,4,9,10-tetrahydro-1H-2-benzoxacyclotetradecine-1,7(8H)-dione	<b>Phase of Development</b> Phase 1/2a
<b>Primary Objective</b> <ul style="list-style-type: none"> <li>• <u>Phase 1</u>: To determine the safety and tolerability of E6201 in subjects with FLT3+ and/or Ras+ AML, MDS or CMML and to establish a recommended Phase 2 dose (RP2D)</li> <li>• <u>Phase 2a</u>: To evaluate the overall response rates (ORR) in subjects who receive E6201 for the treatment of FLT3+ and/or Ras+ relapsed/refractory AML</li> </ul> <b>Secondary Objectives</b> <ul style="list-style-type: none"> <li>• To evaluate duration of response</li> <li>• To evaluate progression-free survival (PFS)</li> <li>• To evaluate overall survival (OS)</li> <li>• To evaluate the pharmacokinetics (PK) of E6201</li> <li>• To explore pharmacodynamic (PD) changes from baseline in signal transduction markers in blood or/and bone marrow: pERK, pFLT3 and pAKT</li> <li>• To explore quantitative changes from baseline in FLT3 internal tandem duplication (FLT3 ITD), FLT3 tyrosine kinase domain (TKD) and Ras+ allelic burden, FLT3 ligand and plasma inhibitory assay (PIA) for FLT3, and evaluate the correlation between FLT3 and Ras+ allelic burden and objective response</li> <li>• To determine the safety and tolerability of E6201 at the RP2D (Phase 2a)</li> </ul>	

**Methodology**

This is a Phase 1/2a, dose-escalation study of E6201, a dual MEK1 and FLT3 inhibitor, in subjects with advanced hematologic malignancies with documented FLT3 and/or Ras mutations. The Phase 1 portion of the study will be conducted as a safety run-in in up to 30 subjects to establish a recommended Phase 2 dose (RP2D).

The Phase 2a portion of the study will evaluate three specific patient groups: Cohort 1 will enroll up to 26 patients with relapsed or refractory AML and confirmed FLT3 mutation (with or without a Ras mutation) without prior exposure to a FLT3 inhibitor, Cohort 2 will enroll up to 26 patients with relapsed or refractory AML and confirmed FLT3 mutation (with or without a Ras mutation) with prior exposure to a FLT3 inhibitor, and Cohort 3 will enroll up to 10 patients with relapsed or refractory AML with a confirmed Ras mutation and no FLT3 mutation. Cohorts 1 and 2 of the expansion phase will incorporate a Simon 2-stage optimal design.

A total of up to N= 92 subjects will be enrolled in the study.

Major selection criteria are: age  $\geq 18$  years with confirmed diagnosis of FLT3+ and/or Ras+ higher-risk MDS/CMML (Phase 1 only), or relapsed or refractory AML with a FLT3 and/or Ras mutation. In the absence of rapidly-progressing disease,  $\geq 3$  weeks after prior cancer treatment for the disease under study, with the exception of hydroxyurea to control peripheral blast counts allowed during the first 2 cycles. Subjects must have recovered from all acute toxicities ( $\leq$  Grade 1), have adequate renal and hepatic function, and no known history of significant cardiac disease.

Phase 1 (Safety Run-In): Following Screening, a total of up to 30 subjects in up to 5 dose cohorts will be enrolled to establish the RP2D. The safety run-in phase will be a standard 3+3 cohort design.

Dose Level 1: 240 mg/m<sup>2</sup> weekly Days 1, 8, 15 and 22, repeated every 28 days (=1 cycle)

Dose Level 2: 320 mg/m<sup>2</sup> weekly Days 1, 8, 15 and 22, repeated every 28 days

Dose Level 3: 160 mg/m<sup>2</sup> twice weekly Days 1, 4, 8, 11, 15, 18, 22 and 25, repeated every 28 days (=1 cycle)

Dose Level 4: 240 mg/m<sup>2</sup> twice weekly Days 1, 4, 8, 11, 15, 18, 22 and 25, repeated every 28 days (=1 cycle)

Dose Level 5: 320 mg/m<sup>2</sup> twice weekly Days 1, 4, 8, 11, 15, 18, 22 and 25, repeated every 28 days

In the first cohort, the dose of E6201 will be 240 mg/m<sup>2</sup>, administered as an intravenous (IV) infusion over 2 hours once weekly (*Dose Level 1*), on Days 1, 8, 15 and 22 of a 28-day schedule (=1 cycle). A minimum of 3 subjects will be treated. If 1 of 3 subjects experiences DLT during Cycle 1, the cohort will be expanded to 6. If  $\geq 2$  of 6 subjects experiences DLT by Day 28, no dose escalation to Dose Level 2 will occur. However, if 0 of 3 or  $\leq 1$  of 6 subjects treated at Dose Level 1 experience DLT by Day 28, dose escalation will proceed to the next cohort, 320 mg/m<sup>2</sup> weekly (*Dose Level 2*), administered by IV infusion over 2 hours on Days 1, 8, 15 and 22 of a 28-day schedule. A minimum of 3 subjects will be treated at this dose level. If 1 of 3 subjects treated at Dose Level 2 experiences DLT during Cycle 1, the cohort will be expanded to 6 subjects. If  $\geq 2$  of 6 subjects experience DLT by Day 28, no further dose escalation will occur.

However, if 0 of 3 or  $\leq 1$  of 6 subjects treated at Dose Level 2 experience DLT by Day 28, dose escalation will proceed to the next dose cohort, 160 mg/m<sup>2</sup> administered as

**Methodology (continued)**

an IV infusion over 2 hours twice weekly (*Dose Level 3*), on Days 1, 4, 8, 11, 15, 18, 22 and 25 of a 28-day schedule (=1 cycle). A minimum of 3 subjects will be treated at this dose level. If 1 of 3 subjects treated at Dose Level 3 experiences DLT during Cycle 1, the cohort will be expanded to 6 subjects. If  $\geq 2$  of 6 subjects experience DLT by Day 28, no further dose escalation will occur.

However, if 0 of 3 or  $\leq 1$  of 6 subjects treated at Dose Level 3 experiences DLT by Day 28, dose escalation will proceed to the next dose cohort, 240 mg/m<sup>2</sup> administered as an IV infusion over 2 hours twice weekly (*Dose Level 4*), on Days 1, 4, 8, 11, 15, 18, 22 and 25 of a 28-day schedule. A minimum of 3 subjects will be treated at this dose level. If 1 of 3 subjects treated at Dose Level 4 experiences DLT during Cycle 1, the cohort will be expanded to 6 subjects. If  $\geq 2$  of 6 subjects experience DLT by Day 28, no further dose escalation will occur.

However, if 0 of 3 or  $\leq 1$  of 6 subjects treated at Dose Level 4 experiences DLT by Day 28, dose escalation will proceed to the next dose cohort, 320 mg/m<sup>2</sup> administered as an IV infusion over 2 hours twice weekly (*Dose Level 5*), on Days 1, 4, 8, 11, 15, 18, 22 and 25 of a 28-day schedule. A minimum of 3 subjects will be treated at this dose level. If 1 of 3 subjects treated at Dose Level 5 experiences DLT during Cycle 1, the cohort will be expanded to 6 subjects. If there are  $\leq 1$  of 6 subjects with DLT at Dose Level 5, this dose (320 mg/m<sup>2</sup> twice weekly) will be declared the MTD and RP2D. If, however,  $\geq 2$  of 6 subjects experiences DLT, then either 320 mg/m<sup>2</sup> weekly (*Dose Level 2*) or 240 mg/m<sup>2</sup> twice weekly (*Dose Level 4*) will be declared the MTD and RP2D based on additional factors (e.g., PK and PD parameters).

Dose-limiting toxicity will be defined as any one of the following events: prolonged myelosuppression (as defined by the National Cancer Institute [NCI] criteria specific for leukemia, i.e., marrow cellularity  $< 5\%$  at  $\geq 6$  weeks from start of therapy without evidence of leukemia);  $\geq$  Grade 3 non-hematologic toxicity (excluding Grade 3 nausea, vomiting or diarrhea that is adequately controlled with supportive care and resolves to  $\leq$  Grade 2 within 48 hours, or Grade 3 electrolyte disturbances responsive to correction within 24 hours);  $\geq$  Grade 3 liver function tests (LFTs) lasting  $> 7$  days; treatment interruption  $> 14$  days due to toxicity; or other important medical event.

Phase 2a (Expansion): Once the Phase 1 Safety Run-In portion of the study is complete and an RP2D is established, additional subjects will be enrolled into the Phase 2 Expansion portion in three cohorts. Cohort 1 will enroll up to 26 patients with relapsed or refractory AML and confirmed FLT3 mutation (with or without a Ras mutation) without prior exposure to a FLT3 inhibitor. Cohort 2 will enroll up to 26 patients with relapsed or refractory AML and confirmed FLT3 mutation (with or without a Ras mutation) with prior exposure to a FLT3 inhibitor. Cohort 3 will enroll up to 10 patients with relapsed or refractory AML with a confirmed Ras mutation and no FLT3 mutation. Cohorts 1 and 2 of the Expansion Phase will incorporate a Simon 2-stage optimal design. Subjects with AML enrolled in the Phase 1 portion of the study at the RP2D will count towards the Phase 2a accrual for the appropriate cohort.

During the study, a Safety Review Committee (SRC), consisting of the actively recruiting investigators, the Medical Monitor and Strategia Therapeutics will review data from each cohort on an ongoing basis.

Subjects will receive E6201 weekly or bi-weekly on a 28-day schedule, with the schedule and dose level established during the safety run-in portion of the study. Disease assessments, including analysis of blood and bone marrow aspirates, will be performed at the end of Cycles 1 and 3 and every 2 cycles thereafter. Disease assessments may be

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<p><b>Methodology (continued)</b></p> <p>made at other time points at the discretion of the Investigator.</p> <p>Subjects who demonstrate clinical benefit (objective response or stable disease) will be allowed to continue therapy with E6201 until progression of disease, observation of unacceptable adverse events, intercurrent illness or changes in the patient's condition that prevents further study participation.</p> <p>Subjects will be instructed to contact their study doctor for ophthalmic evaluation should they experience disturbances in their vision.</p> <p>ECGs will be taken within 28 days prior to Cycle 1, and Days 1 and 15 of each cycle, pre-dose, 5 minutes following the end of the infusion, 2, 4 and 24 hours post-infusion, and at the End-of-Study visit.</p> <p>Blood for hematology and serum chemistry will be collected within 28 days prior to Cycle 1 Day 1, on Days 1, 8, 15 and 22 of Cycle 1, on Day 1 of each subsequent cycle and at the End-of-Study visit.</p> <p>Blood samples for PK assessment of E6201 concentrations will be collected on Cycle 1 Days 1 and Day 15, and Cycle 2 Day 1 pre-dose, 5 minutes following the end of the infusion, 2, 4, 8 and 24 hours post-infusion.</p> <p>Blood samples for PD assessment will be collected at Cycle 1, Days 1 and 15 and Cycle 2 Day 1, pre-dose, 4 and 24 hours post-infusion.</p> <p>Bone marrow will be collected pre-study, at the end of Cycle 1, every 2 cycles thereafter, and at disease relapse/progression, unless the peripheral blood absolute blast count is <math>\geq 5.0 \times 10^9</math> cells/L, to assess mutational status and potentially PD markers.</p>	
<p><b>Number of Subjects and Centers</b></p> <p><u>Phase 1</u>: Up to 30 subjects are planned for the Safety Run-in portion of the study.</p> <p><u>Phase 2a</u>: Up to 26 subjects are planned for Cohort 1 of the Expansion portion, 26 subjects for Cohort 2 and up to 10 subjects for Cohort 3 (total N=62), for a total of up to 92 subjects.</p> <p>The study will be conducted at The University of Texas M.D. Anderson Cancer Center with Gautam Borthakur, M.D. serving as Study Chair. Additional clinical sites include Moffitt Cancer Center (Kendra Sweet, MD), Health ONE Cares (Michael Maris, MD) and Methodist Hospital, San Antonio (Jose Cruz, MD). Additional sites may be added to complete study enrollment in a timely manner.</p>	
<p><b>Duration of Study</b></p> <p>The accrual phase for the Phase 1 Safety Run-in portion is expected to be 24 – 27 months. The expected accrual for the Phase 2a Expansion portion is expected to be 12 months, for a total accrual period of 36 – 39 months. With the last subject followed for up to 6 months, a total study duration of 42 – 45 months is anticipated. The anticipated accrual rate for the Phase 2a portion is 4 – 6 subjects per month across all sites.</p>	

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<b>Inclusion Criteria</b> <ul style="list-style-type: none"> <li>• Males and females <math>\geq 18</math> years of age</li> <li>• <u>Phase 1</u>: Subjects with confirmed relapsed or refractory AML with a documented FLT3 and/or Ras mutation, or age <math>\geq 60</math> years with newly diagnosed FLT3+ and/or Ras+ AML and not eligible for standard induction chemotherapy, or FLT3+ and/or Ras+, higher-risk MDS/CMML (defined as <math>\geq 10\%</math> marrow blasts <u>or</u> <math>\geq 5\%</math> peripheral blood blasts <u>or</u> Revised International Prognostic Scoring System [IPSS-R] score <math>\geq 3.5</math>), and relapsed or refractory to prior therapy</li> <li>• <u>Phase 2</u>: Subjects with confirmed relapsed or refractory AML with a documented FLT3 and/or Ras mutation, or age <math>\geq 60</math> years with newly diagnosed FLT3+ and/or Ras+ AML and not eligible for standard induction chemotherapy</li> <li>• At least 3 weeks beyond the last cancer treatment for the disease under study, major surgery and recovered from all acute toxicities (<math>\leq</math> Grade 1) by first dose of study drug (C1D1). <i>Hydroxyurea used to control peripheral blast counts is permitted during the first 2 cycles.</i></li> <li>• Adequate performance status: Eastern Cooperative Oncology Group (ECOG) <math>\leq 2</math> (<b>Appendix A</b>)</li> <li>• Adequate renal and hepatic function: <ul style="list-style-type: none"> <li>• Serum creatinine <math>\leq 1.5</math> mg/dL OR calculated creatinine clearance <math>\geq 45</math> mL/minute per the Cockcroft-Gault formula (<b>Appendix B</b>)</li> <li>• Total bilirubin <math>\leq 2</math> times the upper limit of normal (ULN) unless due to Gilbert's disease or thought to be due to underlying AML</li> </ul> </li> <li>• ALT and AST <math>\leq 5</math> times ULN</li> <li>• Negative serum pregnancy test within 14 days prior to the first dose of study therapy for women of child-bearing potential (WCBP), defined as a sexually mature woman who has not undergone a hysterectomy or who has not been naturally post-menopausal for at least 24 consecutive months (i.e., who has had menses any time in the preceding 24 consecutive months). Sexually active WCBP and male subjects must agree to use adequate methods to avoid pregnancy (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study and for 28 days after the completion of study treatment.</li> <li>• Ability to provide written informed consent</li> </ul>	

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<p><b>Exclusion Criteria</b></p> <ul style="list-style-type: none"> <li>History of clinically significant cardiac impairment, congestive heart failure (CHF) New York Heart Association (NYHA) Class III or IV, unstable angina, or myocardial infarction during the previous 6 months, or serious cardiac arrhythmia (<b>Appendix C</b>)</li> <li>QT interval corrected for rate (QTc) &gt; 450 msec for males and &gt; 460 msec for females on the electrocardiogram (ECG) obtained at Screening using Fridericia method for QTc calculation (average of 3 readings)</li> <li>Concomitant medication(s) that may cause QTc prolongation or induce Torsades de Pointes with the exception of anti-microbials used as standard of care to prevent or treat infections and other such drugs that are considered by the Investigator to be essential for the care of the patient (<b>Appendix D</b>). However, if such medications are deemed to be necessary during the study, more intensive ECG monitoring will be added during the period of concomitant drug administration.</li> <li>Presence of active central nervous system (CNS) leukemia. Subjects adequately treated for CNS leukemia documented by 2 consecutive cerebrospinal fluid samples negative for leukemia cells are eligible. Subjects with no history of CNS leukemia will not be required to undergo cerebrospinal fluid sampling for eligibility.</li> <li>Known positive for human immunodeficiency virus (HIV), hepatitis B virus surface antigen (HBsAg), or hepatitis C virus (HCV)</li> <li>Active, uncontrolled infection</li> <li>Known hypersensitivity to any study drug component</li> <li>History of another malignancy; <i>Exception:</i> Patients disease-free for 2 years or treated <i>in situ</i> carcinoma</li> <li>Any other medical intervention or other condition which, in the opinion of the Principal Investigator, could compromise adherence to study requirements or confound the interpretation of study results</li> <li>Pregnancy or lactation</li> </ul>	



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<b>Criteria for Evaluation</b> <b>Safety</b> Safety will be assessed through the monitoring of adverse events (AEs), clinical laboratory parameters (hematology and serum chemistry), vital sign measurements, ECGs and physical examinations. Adverse events will be classified according to the Medical Dictionary for Regulatory Affairs (MedDRA) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. <b>Efficacy</b> Efficacy assessment for AML will be performed using a modification of the recommendations of the International Working Group (IWG) for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Efficacy assessments for subjects with MDS or CMML will be performed using a modification of the IWG Response Criteria in Myelodysplasia. <b>Pharmacokinetics</b> Pharmacokinetic determinations of E6201 in plasma will be made. <b>Pharmacodynamics</b> Levels of pERK, pFLT3, pAKT, FLT3 ITD, FLT3 TKD and Ras+ allelic burden, FLT3 ligand and plasma inhibitory assay (PIA) for FLT3, will be measured in blood and/or bone marrow samples collected from each subject. Additional markers or mutation analysis will be undertaken, if needed.	
<b>Investigational Product</b> E6201 for Injection is a natural product analog and novel inhibitor of FMS-like tyrosine kinase-3 (FLT3) and mitogen-activated protein kinase/extracellular-signal regulated kinase kinase-1 (MEK1). It is a sterile white lyophilized powder containing 60 mg of E6201 formulated in cyclodextrin to improve E6201 solubility in water. E6201 for Injection is packaged in a 15-mL or 20-mL capacity Type I glass vial with a bromobutyl rubber stopper and an aluminum cap. Reconstituted and diluted E6201 solutions should be stored refrigerated (2 to 8°C) and protected from light before administration.	
<b>Reference therapy</b> None	
<b>Statistical Methods</b> <b>Efficacy Endpoints and Analyses</b> The primary endpoint will be the proportion of patients who achieve an objective response (OR) as best response within 3 cycles of treatment with E6201. Each Phase 1 dose cohort will be analyzed independently; each Phase 2a disease cohort will be analyzed independently. The number and percentage of subjects with an OR will be summarized. For secondary endpoints, duration of response, PFS and OS curves will be estimated using the Kaplan-Meier product-limit estimates.	

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<p><b>Statistical Methods (continued)</b></p> <p><b><i>Pharmacokinetic Endpoint Analyses</i></b></p> <p>Mean plasma concentrations of E6201 will be determined in blood samples collected before administration of E6201 and at multiple time points after administration of E6201. Because plasma concentrations will be determined at a limited number of time points during the study, a complete pharmacokinetic profile of E6201 at each dose level will not be possible. Limited pharmacokinetic analyses will be performed.</p> <p><b><i>Pharmacodynamic Endpoint Analyses</i></b></p> <p>Changes from baseline in levels of pERK, pFLT3, pAKT, FLT3 ITD, FLT3 TKD and Ras+ allelic burden, FLT3 ligand and PIA for FLT3, and will be measured in blood and/or bone marrow samples collected from each subject at multiple points during the study. Changes from baseline in pERK and pFLT3 will be measured in bulk and progenitor cells. Correlation between FLT3 and Ras+ allelic burden, pharmacokinetics and clinical response will be assessed.</p> <p>Changes from baseline in PD parameters for each cohort will be summarized using descriptive statistics, including number of patients (N), mean, standard deviation (SD), minimum, median, maximum range, and coefficient of variation (CV). Additional or other genomic changes may be evaluated.</p> <p><b><i>Safety Endpoints and Analyses</i></b></p> <p>Safety endpoints for adverse events (AEs) include the following: incidence of all treatment-emergent AEs (TEAEs) and all serious AEs (SAEs); by severity, relationship to study medication, Grade 3 and 4 TEAEs, discontinuation of subjects from study due to AEs or death. Safety endpoints for AEs, clinical laboratory tests, vital signs, physical examinations and ECGs will be specified in the statistical analysis plan. Safety summaries will be provided by each cohort independently, and for the combined safety population representing all cohorts.</p>	

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**LIST OF ABBREVIATIONS**

<b>Abbreviation</b>	<b>Definition</b>
AE	Adverse event
ALT (SGPT)	Alanine transaminase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase
BUN	Blood urea nitrogen
C	Centigrade
CFR	Code of Federal Regulations
C <sub>max</sub>	Peak concentration
CML	Chronic myelocytic leukemia
CMML	Chronic myelomonocytic leukemia
CNS	Central nervous system
CR	Complete remission
Cri	Complete remission with incomplete blood count recovery
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
CYP	Cytochrome P450
dL	Decaliter
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full analysis set
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase-3
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HbsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICD	Informed consent document

<b>Abbreviation</b>	<b>Definition</b>
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IPSS-R	Revised International Prognostic Scoring System
IRB	Institutional Review Board
ITD	Internal tandem duplication
IV	Intravenous
IWG	International Working Group
Kg	Kilogram
L	Liter
LDH <sub>0</sub>	Lactate dehydrogenase
m <sup>2</sup>	Meters squared
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase
Mg	Milligram
mL	Milliliter
μ	Micro
M	Molar
MTD	Maximum tolerated dose
N	Number
NCI	National Cancer Institute
NOAEL	No adverse effect level
NOG	Non-obese diabetic gamma null
NYHA	New York Heart Association
OR	Objective response
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic, progressive disease
PFS	Progression-free survival
PI	Principal Investigator
PIA	Plasma inhibitory assay
PK	Pharmacokinetic
PPS	Per protocol set
PR	Partial remission
QTc	QT interval corrected for rate
RBC	Red blood cell



<b>Abbreviation</b>	<b>Definition</b>
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SD	Standard deviation, stable disease
SRC	Safety Review Committee
T <sub>1/2</sub>	Half-life
TEAE	Treatment-emergent adverse event
TKD	Tyrosine kinase domain
TKI	Tyrosine kinase inhibitor
T <sub>max</sub>	Time to peak concentration
U	Units
UDS	Unscheduled DNA synthesis
ULN	Upper limit of normal
WBC	White blood cell
WCBP	Woman of child-bearing potential

## 1. INTRODUCTION

### 1.1. Oncogenic Growth Stimulatory Pathways in Hematologic Malignancies

Survival of acute myeloid leukemia (AML) and other malignant cells is dependent to variable degrees on mutational activation of oncogenic pathways. This is evidenced by clinical activity of single-agent FLT3 inhibitors observed in patients carrying FMS-like tyrosine kinase 3 (FLT3) mutations (30% of AML) and of mitogen-activated protein kinase (MEK) inhibitors in patients carrying either K or N-Ras mutations (~25 – 40% of AML).<sup>1-4</sup> Constitutive phosphorylation and subsequent activation of FLT3 is observed in patients carrying either internal tandem duplication (ITD) or point (D835) mutation in the FLT3 gene. AML associated with FLT3 mutation, in particular the FLT3 internal tandem duplication (ITD) mutation, is associated with poor overall prognosis and event-free survival in a group of relatively younger patients with AML.<sup>5-8</sup>

The Ras/Raf signaling pathway signals through the downstream signal transducers MEK1 and ERK and is relevant in FLT3 mutated AML. Activation of this pathway as evidenced by ERK phosphorylation is present constitutively and more importantly is seen in AML cells of patients failing FLT3 inhibitor therapy even when FLT3 phosphorylation remains suppressed (data from MDACC). Activating Ras mutations are also encountered in 10-15% of patients with AML. While the direct clinical association between Ras mutations and clinical outcome in AML is not as clearly documented as with FLT3 mutations, clinical data clearly show that ERK phosphorylation, a downstream mediator of Ras signaling, in AML cells is linked to poor clinical outcome in patients with AML.<sup>9</sup>

### 1.2. Single Agent Clinical Activity of Kinase Inhibitors Targeting FLT3 or MEK in Hematologic Malignancies

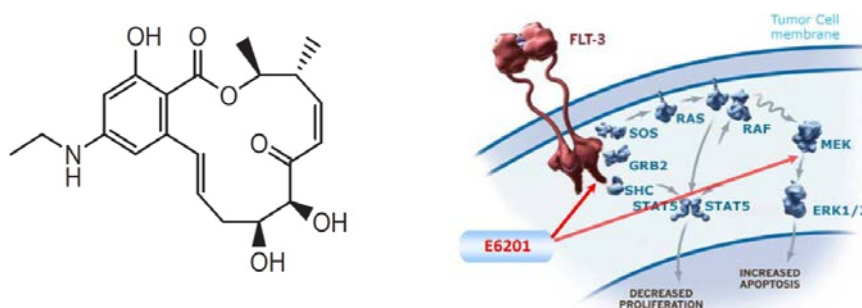
Kinase inhibitors targeting FLT3 or MEK have shown clear clinical activity, including complete remissions, in patients with AML harboring relevant activating mutations. A phase 2 study of quizartinib (AC220) in patients with relapsed/refractory AML associated with FLT3-ITD mutation showed a composite CR rate of 45% and partial remission (PR) rate of 24%.<sup>2</sup> Trametinib (GSK1120212) demonstrated a CR/CRp rate of 25% in patients with relapsed/refractory AML and myelodysplastic syndrome (MDS) associated with Ras mutation.<sup>3</sup> Unfortunately the remissions in patients with AML and MDS receiving selective tyrosine kinase inhibitors (TKIs) are relatively short-lasting.<sup>10,11</sup> Furthermore, cells resistant to FLT3-ITD inhibitors sorafenib and quizartinib can acquire resistant point mutations of FLT3 in the tyrosine kinase domain in addition to the ITD mutation.<sup>12</sup>

### 1.3. Hypothesis and Rationale for Dual Pathway Inhibition in Hematologic Malignancies

Responses to agents that act on single signaling pathways are of relatively short duration, suggesting emergence of resistance which may be mediated through parallel activation of multiple signaling pathways<sup>9,13</sup> and which may be overcome by simultaneous targeting of multiple signaling pathways. Because activation of parallel signaling pathways can contribute to development of resistance to FLT3 inhibitors, we hypothesize that simultaneous inhibition of both the FLT3 and MEK signaling pathways will provide a mechanism to overcome resistance that occurs via activation of parallel growth stimulatory and survival pathways.

#### 1.4. E6201, a Dual MEK1/FLT3 Inhibitor to Overcome Resistance to Single-Pathway Inhibitors

E6201 is a natural product analog that inhibits both MEK1 and FLT3. This dual inhibition activity is anticipated to provide a mechanism to overcome resistance that occurs via activation of parallel growth stimulatory and survival pathways. The chemical structure and mechanism of action of E6201 are depicted in **Figure 1**.



**Figure 1. Chemical Structure and Mechanism of Action of E6201**

##### 1.4.1. *In Vitro and In Vivo Pharmacology of E6201*

E6201 is a dual MEK1/FLT3 inhibitor with activity against both targets reportedly in the low nanomolar range. E6201 shows identical affinity and residence time for active and inactive forms of MEK1. While affinity for FLT3 is lower, the residence time for FLT3 is 11-fold higher than for MEK1, thus making this compound an effective inhibitor for both MEK1 and FLT3.

To verify the hypothesis that concomitant pathway inhibition could achieve longer lasting antitumor activity, E6201 was tested in a series of studies described below.<sup>14</sup>

E6201 was tested against AML cell lines (including FLT3-inhibitor resistant cells), primary AML patient samples, and in a murine AML model. The AML cell lines examined in this study are depicted in **Table 1**.

**Table 1. AML Cell Lines Examined**

Cell Line	Type	FLT3 Status	Ras Status
OCI/AML3	Myeloid Leukemia	N/A	N-Ras/61
THP-1	AML M4	FLT3-wt	N-Ras/12
Kasumi-1	AML M2	FLT3-wt	K-Ras/12
MOLM13	AML	FLT3/ITD	WT
MV4-11	Biphenotypic Leukemia	FLT3/ITD	WT
Ba/F3-FLT3	murine AML	hFLT3-wt	WT
Ba/F3-ITD	murine AML	hFLT3/ITD	WT
Ba/F3-D835G	murine AML	hFLT3/D835G	WT
Ba/F3-ITD+676/842	murine AML	hFLT3/ITD, N676D, Y842C	WT
Ba/F3-ITD-Res	murine AML	hFLT3/ITD, N676D, Y842C	WT

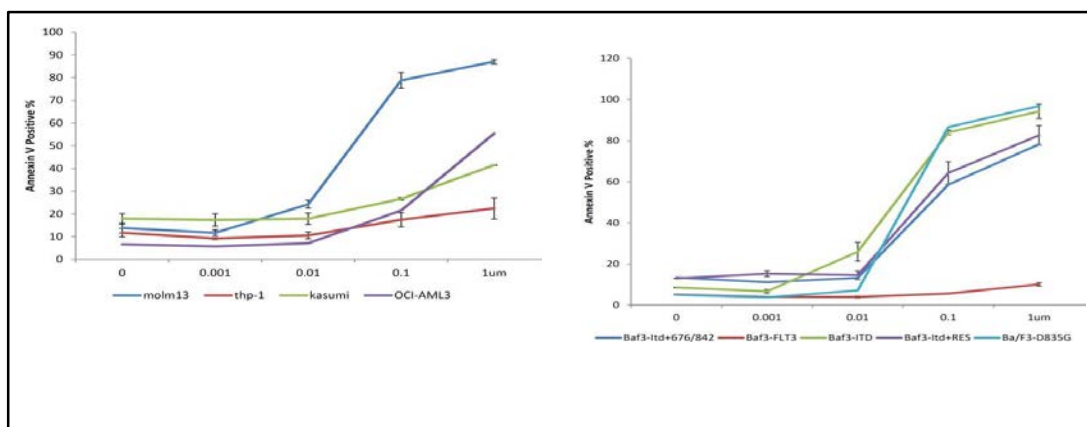
E6201 inhibited cell growth and induced apoptosis in AML cells with FLT3 ITD mutations

(including sorafenib-resistant cells harboring ITD plus N676D/Y842C point mutations) at nanomolar concentrations, and showed 600- to 1000-fold more selective activity against cells with FLT3-ITD mutations than those with FLT3-Wild Type (WT), with  $IC_{50}$  of 0.003, 0.005 and 0.002  $\mu$ M against Ba/F3-ITD, FLT3-ITD mutant MOLM13 and MV4-11 cells, respectively, compared to 3.18  $\mu$ M in Ba/FLT3-WT cells. Notably, dual FLT3-WT/RAS mutant OCI/AML3 cells, with high basal p-ERK level and with resistance to most chemotherapeutic agents, were sensitive to E6201, with  $IC_{50}$  = 0.037  $\mu$ M (**Table 2**).

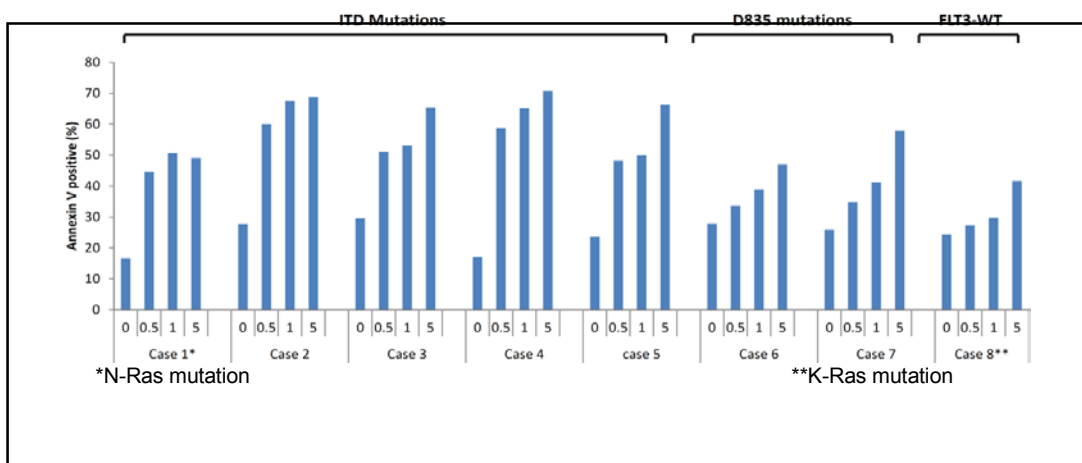
**Table 2.  $IC_{50}$  of E6201 in Multiple Types of AML Cells**

$IC_{50}$ ( $\mu$ m)	Dm	lower 95%	upper 95%
OCI-AML3	0.037	0.0091	0.182
THP-1	0.67	0.11	4.17
Kasumi-1	0.37	0.11	1.22
molm13	0.00485	0.00303	0.00712
MV4-11	0.0019	1.26E-05	0.25209
Ba/F3-ITD	0.00319	0.00244	0.00415
Ba/F3-ITD+676/842	0.00555	0.00017	0.18
Ba/F3-ITD-RES	0.0159	0.00769	0.0329
Ba/F3-D835G	0.0046	0.0018	0.0119
Ba/F3-FLT3	3.18	1.96	5.16

Apoptosis was determined via FACS analysis by measuring annexin V-positivity at 72 hours. The  $IC_{50}$  of E6201 was sub-micromolar in all 5 FLT3-ITD mutant primary AML samples, which included one with FLT3-ITD/RAS dual mutation (**Figures 2 and 3**).

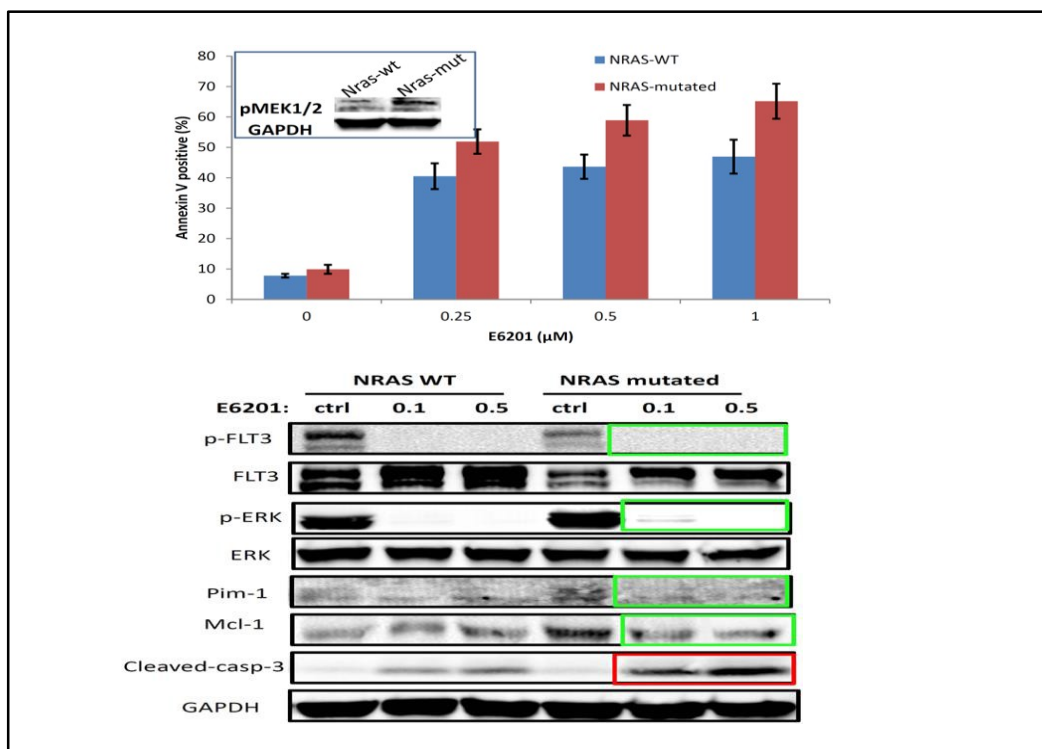


**Figure 2. E6201 Exerts Cytotoxic Effects in AML Cells with FLT3 or *N*-Ras Mutations**



**Figure 3. E6201 Induces Apoptosis in FLT3-ITD-mutated Primary AML Cells *Ex vivo***

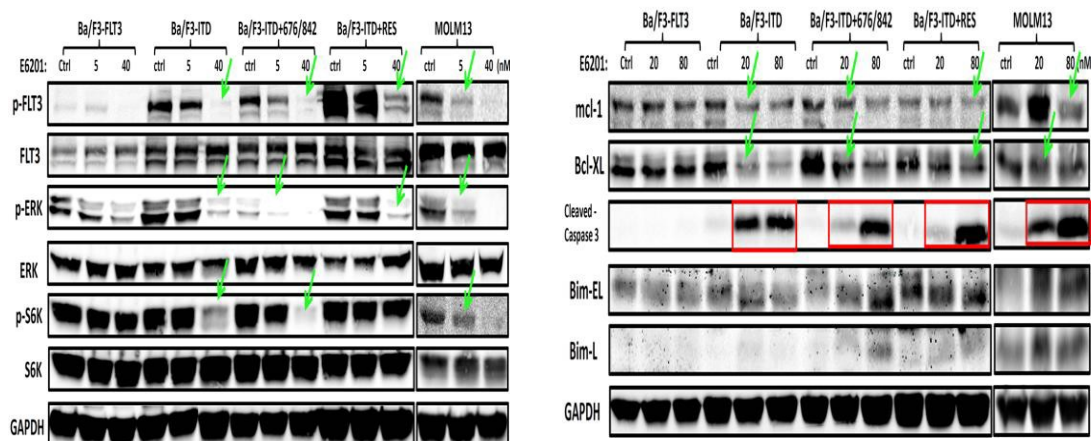
Consistent with its MEK1 inhibitory activity, E6201 was more active against NRAS mutant MV4-11 cells than its NRAS-WT isogenic counterpart (**Figure 4**).



**Figure 4. E6201 Enhanced Cytotoxicity in N-Ras Mutated Leukemia Cells by Suppression of Pim-1 and Mcl**

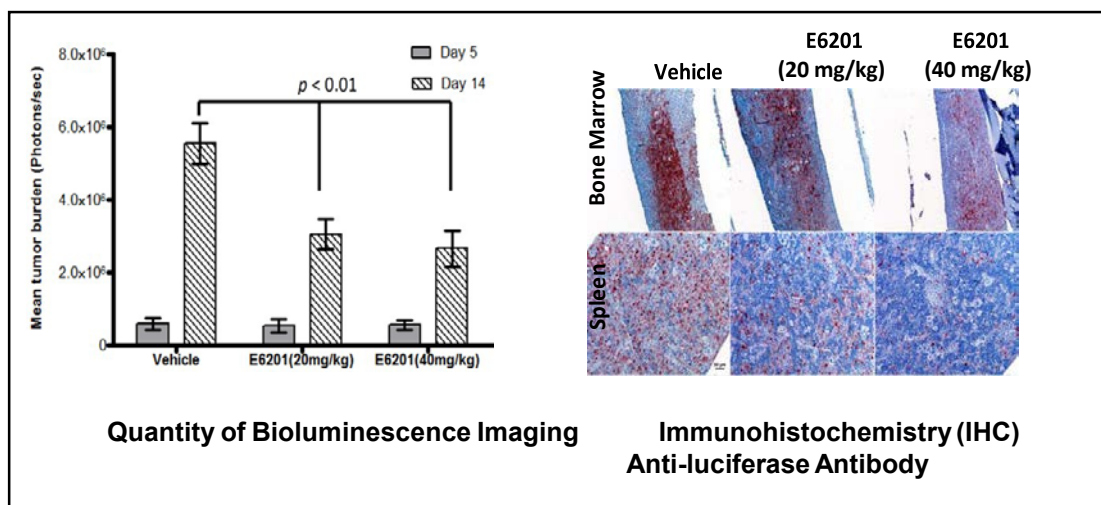
Mechanistically, E6201 markedly suppressed p-FLT3 and p-ERK in all tested FLT3 mutant AML cell lines and in N-Ras mutant OCI/AML3 cells.

In addition, decreased Bcl-xL and Mcl-1 levels (green arrows) and increased cleaved-caspase-3 (red boxes) were observed in all FLT3 mutant cell lines after treatment with E6201 for 1 hour (left panel) and 24 hours (right panel) (**Figure 5**).



**Figure 5. E6201 Modulation of Apoptosis Via Signaling Proteins and Bcl-2**

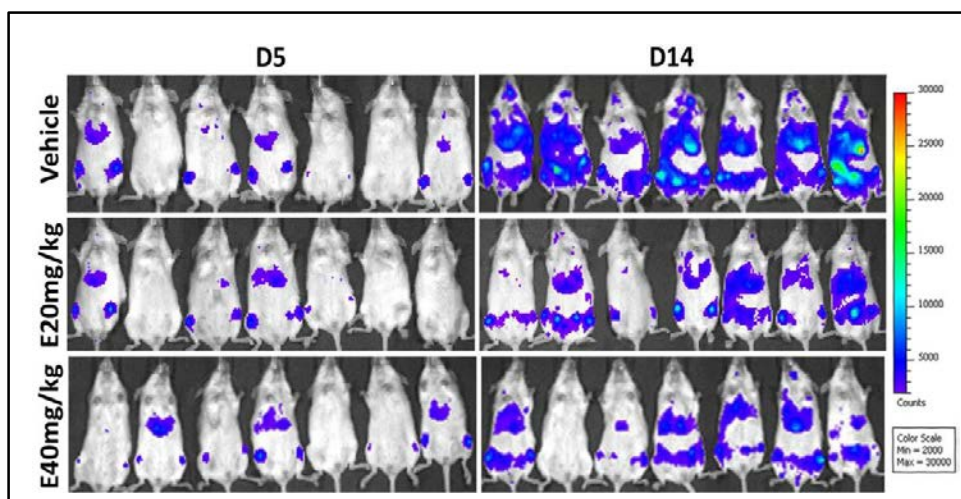
Non-obese diabetic gamma null (NOG) mice bearing xenografts of MOLM13-Luc-GFP (FLT3-ITD mutated) cells were treated with E6201 intravenously (IV) on a twice weekly schedule from Day 5 after leukemia cell injection until Day 21. Bioluminescence imaging revealed profound reductions in tumor burden and leukemia cell infiltration in groups receiving E6201 at 20 or 40 mg/kg versus vehicle control;  $3.1 \times 10^6$ ,  $2.7 \times 10^6$  versus  $5.6 \times 10^6$  photons/sec, respectively ( $p < 0.01$ ). The bioluminescence imaging was confirmed by immunohistochemistry with an anti-luciferase antibody in spleen and bone marrow specimens (**Figure 6**).



**Figure 6. E6201 Blocks Leukemia Progression in a MOLM13 Murine Xenograft Model**

Leukemia cell infiltration was markedly reduced in bone marrow, spleen, liver and lungs starting on Day 9 after the first E6201 dose (Day 5 and 14 shown below in **Figure 7**).





**Figure 7. E6201 Reduces Leukemia Cell Infiltration in Progression in Murine Xenograft Model with MOLM13 Cells**

E6201 has been extensively studied in preclinical IND-enabling studies performed by Eisai Pharmaceuticals. An Investigator's Brochure is available that describes these studies in more detail.<sup>15</sup>

#### **1.4.2. Safety Pharmacology**

*In vivo* studies of E6201 administered as a 30-minute intravenous infusion at doses up to 60 mg/kg in rats had no effects on the central nervous system (CNS) or on respiratory function. In dogs, doses of E6201 up to 30 mg/kg (in 18% – 30% Captisol formulation) administered as a 30-minute intravenous infusion showed no effects on heart rate (HR), blood pressure (BP) or electrocardiogram (ECG) parameters. The maximum observed plasma concentration ( $C_{max}$ ) was estimated to be 16169.24 ng/mL in the male rat and 8988.10-15269.67 ng/mL in dogs.

In a 5-minute infusion in anesthetized dogs, both vehicle (30% Captisol®) and E6201 (6-30 mg/kg in 30% Captisol) exhibited effects on cardiopulmonary function, including increases in mean BP, systolic left ventricular pressure, left ventricular end-diastolic pressure, mean right atrial pressure, mean pulmonary artery pressure, pulmonary artery wedge pressure, and cardiac output. These effects were attributed to the physiochemical properties of Captisol (high osmolality and viscosity) and were not observed after 30-minute intravenous infusion, except for a 36.5% increase in cardiac output observed with E6201 at 30 mg/kg in 30% Captisol solution, compared to vehicle alone (30% Captisol). Doses of E6201 up to 18 mg/kg in 18% Captisol solution administered as a 30-minute intravenous infusion had no effects on cardiopulmonary function.

#### **1.4.3. Pharmacokinetics and Metabolism**

After oral or intravenous administration, the PK of E6201 in mice, rats, and rabbits was characterized by moderately extensive distribution, rapid clearance (CL) and elimination. No gender differences were found in either rat (up to 60 mg/kg) or dog (30 mg/kg) toxicokinetic studies after intravenous dosing. In *in vitro* studies, E6201 did not inhibit or induce the major human cytochrome P450 (CYP) isoenzymes.

#### **1.4.4. Nonclinical Toxicology**

##### **1.4.4.1. Single-Dose Toxicity in Rats and Dogs**

Doses up to 60 mg/kg E6201 in Captisol solution administered as single intravenous (IV) bolus injections to rats produced pulmonary toxicity. Decreased activity and/or ptosis were observed at doses of 20 or 60 mg/kg E6201, which disappeared within 1 day. The incidence of mortality was 1/40 (2.5%) and 4/76 (5.3%) at 20 and 60 mg/kg, respectively. In animals with severe clinical signs, histopathological findings of perivascular edema/hemorrhage and alveolar edema were observed, with death due to acute pulmonary edema. No degenerative changes in the alveoli or cardiac histopathological findings were observed. These effects were obviated by changing the mode of administration from a bolus injection to a 30-minute infusion; E6201 is thought to have little direct effect itself on the lung. In a single intravenous bolus toxicity study in dogs (6, 18, or 30 mg/kg doses), E6201-related clinical signs were limited to transient decreased activity and abnormal gait at 30 mg/kg. In a PK study, gastrointestinal toxicity and deteriorating physical condition were observed at 30 mg/kg.

##### **1.4.4.2. Repeat-Dose Toxicity in Rats and Dogs**

In repeat-dose IV toxicity studies in rats and dogs (every 7 days over a 15-day period), no E6201-related effects were observed in rats, while limited clinical signs of transient tremors, salivation and emesis were observed in dogs at doses  $\geq 18$  mg/kg without any clinical pathological or histopathological correlates. E6201 (10 or 30 mg/kg) administered intravenously once a day for 4 days to male and female Beagle dogs resulted in no deaths, no test article-related abnormal clinical signs, no toxicologically significant changes in body weights, food consumption, hematology, blood chemistry, or macroscopic pathology.

##### **1.4.4.3. Genotoxicity**

E6201 was negative in the reverse mutation assay in bacteria (Ames test) and in the *in vivo* rat micronucleus and unscheduled DNA synthesis (UDS) tests. The genotoxic risk of E6201 in humans is, therefore, considered low.

##### **1.4.4.4. Reproductive and Developmental Toxicity**

E6201 was positive in studies of maternal and fetal toxicity. The NOAEL for maternal toxicity and embryo-fetal development in pregnant rats and rabbits was 6 mg/kg. In rats, the no adverse effect level (NOAEL) for maternal toxicity was 6 mg/kg and 2 mg/kg for reproduction and early embryo development. Therefore, precautions will be taken to avoid pregnancy in the proposed clinical study.

#### **1.5. E6201 for Injection Clinical Experience**

Eisai Co., Ltd. was developing E6201 for Injection for patients with cancer and E6201 topical cream for dermatologic indications. The information summarized below is for E6201 for Injection. Please refer to the Investigator's Brochure for more information.<sup>15</sup>

##### **1.5.1. Phase 1 Study in Advanced Melanoma (E6201-A001-102)**

The safety and tolerability of E6201 for Injection was investigated by Eisai Co., Ltd. In Protocol E6201-A001-102, a Phase 1, multicenter, open-label, dose-escalation, safety, pharmacokinetic and pharmacodynamic study in subjects with advanced melanoma. The study, which is now closed to enrollment, had 2 parts: Part A (Dose Escalation) and Part B (Expansion). A total of 25 subjects with advanced solid tumors were enrolled in Part A and



30 subjects with BRAF-mutated melanoma or wild-type melanoma were enrolled in Part B for a total of 55 subjects.

#### 1.5.1.1. Most Frequently Observed Adverse Events

In the dose escalation portion of the study, the primary endpoint was determination of the maximum tolerated dose (MTD) of E6201. Twenty-five subjects received E6201 in dosing cohorts of 20, 40, 80, 160, 320, 400 and 480 mg/m<sup>2</sup> E6201 administered by intravenous infusion over 30 minutes once a week on Days 1, 8, and 15 of a 28-day cycle. Treatment-emergent adverse events considered by the Investigator to be probably related to E6201 are listed in **Table 3**. Two subjects had serious adverse events (SAEs) considered by the Investigator to be possibly or probably related to study medication.

**Table 3. Treatment-Emergent Adverse Events Considered by Investigators to be Probably Related to E6201 in the Dose Escalation Part of Study E6201-A001-102**

MedDRA Preferred Term	E6201 Dose Level (mg/m <sup>2</sup> )							
	20 (N=4) n (%)	40 (N=3) n (%)	80 (N=3) n (%)	160 (N=3) n (%)	320 (N=7) n (%)	400 (N=1) n (%)	480 (N=4) n (%)	Total (N=25) n (%)
QTc prolonged	0	0	0	0	1 (14)	0	2 (50)	3 (12)
Amnesia	0	0	0	0	0	0	1 (25)	1 (4)
Confusional state	0	0	0	0	0	0	1 (25)	1 (4)
Disorientation	0	0	0	0	0	1 (100)	0	1 (4)
Dizziness	0	0	0	0	0	1 (100)	0	1 (4)
Feeling abnormal	0	0	0	0	0	0	1 (25)	1 (4)
Nausea	1 (25)		0	0	0	0	0	1 (4)
Tinnitus	0	0	0	0	0	0	1 (25)	1 (4)

#### 1.5.1.2. Dose-Limiting Toxicities

Based on DLT data, summarized in **Table 4**, the MTD of E6201 was determined to be 320 mg/m<sup>2</sup> when administered by intravenous infusion over 30 minutes once a week on Days 1, 8, and 15 of a 28-day cycle.

**Table 4. Dose-Limiting Toxicities of E6201 Administered by Intravenous Infusion over 30 Minutes Once a Week**

Patient Number	E6201 Dose Level at DLT Onset (mg/m <sup>2</sup> )	Adverse Event (Investigator Term)	CTC Grade
10011019	320	QTc Prolongation	2
10011014	480	QTc Prolongation	3
10011015	480	Confusion	4

Thirty (30) patients were enrolled in the dose expansion portion of the study, with 27 receiving E6201 at 320 mg/m<sup>2</sup> by one-hour intravenous infusion once weekly. No DLTs were observed in this group of patients.

#### 1.5.1.3. Adverse and Serious Adverse Events at 320 mg/m<sup>2</sup>

Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)

considered by the Investigator to be related to E6201 when administered at 320 mg/m<sup>2</sup> once weekly in the Phase I study are summarized in **Tables 5 and 6**, respectively.

**Table 5. TEAEs Related to E6201 Administered at 320 mg/m<sup>2</sup>**

MedDRA Preferred Term	Total n (%) (N=34 Subjects)
QTc prolonged	1 (2.7)*
Nausea	3 (8.1)
Vomiting	2 (5.4)
Rash	1 (2.7)
Constipation	1 (2.7)
Fatigue	1 (2.7)
Hypokalemia	1 (2.7)
Neutrophil count decreased	1 (2.7)
Skin hyperpigmentation	1 (2.7)

\* observed in the dose-escalation portion of the Phase I study in which E6201 was administered by infusion over 30 minutes; not observed with 60-minute infusion

**Table 6. Treatment-Emergent Serious Adverse Events Related to E6201 Administered at 320 mg/m<sup>2</sup> over 60 minutes**

MedDRA Preferred Term	Total n (%) (N=34 Subjects)
Uncontrolled hypertension	1 (2.7)

The SAE of uncontrolled hypertension developed during Cycle 2 and resolved without treatment.

#### 1.5.1.4. Pharmacokinetic Profile of E6201

The pharmacokinetic profiles of E6201 and its major metabolite ER-813010 were determined in blood samples collected on Days 1 and 15 of Cycle 1 from patients with advanced solid tumors enrolled in the dose escalation portion of the Phase I study. The PK data for the 7 dosing cohorts in which E6201 was administered by intravenous infusion over 30 minutes at doses ranging from 20 to 480 mg/m<sup>2</sup>, indicate that E6201 undergoes extensive distribution and fast elimination that is independent of dose. E6201 exposure (AUC<sub>0-∞</sub>) increased with increasing dose up to 320 mg/m<sup>2</sup> and was comparable at doses above 320 mg/m<sup>2</sup>. Mean C<sub>max</sub> and AUC<sub>0-∞</sub> were similar between Day 1 and Day 15 at comparable doses of E6201. ER-813010, the isomeric metabolite of E6201, represented 9.5% to 44.9% of the parent compound. Urinary clearance is a minor route of elimination for E6201. For further pharmacokinetic details, please refer to the Investigator's Brochure.<sup>12</sup>

#### 1.5.2. Phase 1/2a Study in Advanced Hematologic Malignancies (BSC-101-01)

The Phase 1/2a, dose-escalation study of E6201 in patients with advanced hematologic malignancies with documented FLT3 and/or Ras mutations is ongoing. As of December 21, 2015, a total of 5 patients had been treated at 240 mg/m<sup>2</sup> weekly (Cohort 1) and 5 patients had been treated at 320 mg/m<sup>2</sup> weekly (Cohort 2) for a total of 10 subjects.

The most frequently reported AEs across all doses in ≥ 2 subjects (≥ 20%) include QTc prolongation, decreased appetite, fatigue, intracranial hemorrhage, sepsis, hypokalemia, acute respiratory failure and sinusitis reported in 2 subjects (20%) each. Febrile

neutropenia and cellulitis were reported in 3 subjects each (30%). E6201-related AEs include QTc prolongation in 1 subject in the 240 mg/m<sup>2</sup> dose group (Grade 3) and in 1 subject in the 320 mg/m<sup>2</sup> dose group (Grade 2) when E6201 was administered over a 1 hour infusion. Both cohorts were expanded to N=6 each, the infusion time lengthened to 2 hours via Amendment 4 to the study protocol and no further events have occurred.

### **1.5.3. Rationale for Phase 1/2a Study of E6201 in FLT3+ and/or Ras+ AML**

In contrast to patients with chronic myeloid leukemia (CML), the remissions in patients with AML and MDS receiving tyrosine kinase inhibitors (TKIs) are relatively short-lasting. Because activation of parallel signaling pathways can contribute to development of resistance to FLT3 and MEK inhibitors, it is hypothesized that simultaneous inhibition of both the FLT3 and MEK signaling pathways with E6201, a dual inhibitor of MEK1 and FLT3, will provide a mechanism to overcome resistance that occurs via activation of parallel growth stimulatory and survival pathways.

E6201 has not caused ophthalmic changes in the 55 patients treated in the E6201-A001-102 study at doses of 20 – 480 mg/m<sup>2</sup> weekly or twice weekly, and 1 of these patients remain on E6201 for ≥ 5 years at a dose of 320 mg/m<sup>2</sup>/week x 3 weeks q 28 days. However, other MEK inhibitors have caused ocular toxicities including retinal vein occlusion, retinal pigment epithelial detachment, uveitis, and iritis, and these findings are believed to be related to the drug class. Since E6201 is a MEK1 and FLT3 inhibitor, patients should contact their study doctor for an ophthalmologic evaluation if they experience visual disturbances.

## **2. STUDY OBJECTIVES**

### **2.1. Primary Objective**

Phase 1: To determine the safety and tolerability of E6201 in subjects with FLT3+ and/or Ras+ AML, MDS or CMML and to establish a recommended Phase 2 dose (RP2D)

Phase 2a: To evaluate the overall response rates (ORR) in subjects who receive E6201 for the treatment of FLT3+ and/or Ras+ relapsed/refractory AML

### **2.2. Secondary Objectives**

- To evaluate duration of response
- To evaluate progression-free survival (PFS)
- To evaluate overall survival (OS)
- To assess the pharmacokinetics (PK) of E6201
- To explore pharmacodynamics (PD) changes from baseline in signal transduction markers in blood or/and bone marrow: pERK, pFLT3 and pAKT
- To explore quantitative changes from baseline in FLT3 internal tandem duplication (FLT3 ITD), FLT3 tyrosine kinase domain (TKD) and Ras+ allelic burden, FLT3 ligand and plasma inhibitory assay (PIA) for FLT3, and evaluate the correlation between FLT3 and Ras+ allelic burden and objective response
- To determine the safety and tolerability of E6201 at the RP2D (Phase 2a)

### 3. INVESTIGATIONAL PLAN

#### 3.1. Overall Study Design

This is a Phase 1/2a, dose-escalation study of E6201, a dual MEK1 and FLT3 inhibitor, in subjects with advanced hematologic malignancies with documented FLT3 and/or Ras mutations. The Phase 1 portion of the study will be conducted as a safety run-in in up to 30 subjects to establish a recommended Phase 2 dose (RP2D).

The Phase 2a portion of the study will evaluate three specific patient groups: Cohort 1 will enroll up to 26 patients with relapsed or refractory AML and confirmed FLT3 mutation (with or without a Ras mutation) without prior exposure to a FLT3 inhibitor, Cohort 2 will enroll up to 26 patients with relapsed or refractory AML and confirmed FLT3 mutation (with or without a Ras mutation) with prior exposure to a FLT3 inhibitor, and Cohort 3 will enroll up to 10 patients with relapsed or refractory AML with a confirmed Ras mutation and no FLT3 mutation. Cohorts 1 and 2 of the expansion phase will incorporate a Simon 2-stage optimal design.

A total of up to N=92 subjects will be enrolled in the study.

Major selection criteria are: age  $\geq 18$  years with confirmed diagnosis of FLT3+ and/or Ras+ higher-risk MDS/CMML (Phase 1 only), or relapsed or refractory AML with a FLT3 and/or Ras mutation. In the absence of rapidly-progressing disease,  $\geq 3$  weeks after prior cancer treatment for the disease under study, with the exception of hydroxyurea to control peripheral blast counts allowed during the first 2 cycles. Subjects must have recovered from all acute toxicities ( $\leq$  Grade 1), have adequate renal and hepatic function, and no known history of significant cardiac disease.

Phase 1 (Safety Run-In): Following Screening, a total of up to 30 subjects in up to 5 dose cohorts will be enrolled to establish the RP2D. The safety run-in phase will be a standard 3+3 cohort design.

Dose Level 1: 240 mg/m<sup>2</sup> weekly Days 1, 8, 15 and 22, repeated every 28 days (=1 cycle)

Dose Level 2: 320 mg/m<sup>2</sup> weekly Days 1, 8, 15 and 22, repeated every 28 days

Dose Level 3: 160 mg/m<sup>2</sup> twice weekly Days 1, 4, 8, 11, 15, 18, 22 and 25, repeated every 28 days

Dose Level 4: 240 mg/m<sup>2</sup> twice weekly Days 1, 4, 8, 11, 15, 18, 22 and 25, repeated every 28 days (=1 cycle)

Dose Level 5: 320 mg/m<sup>2</sup> twice weekly Days 1, 4, 8, 11, 15, 18, 22 and 25, repeated every 28 days

In the first cohort, the dose of E6201 will be 240 mg/m<sup>2</sup>, administered as an intravenous (IV) infusion over 2 hours once weekly (*Dose Level 1*), on Days 1, 8, 15 and 22 of a 28-day schedule (=1 cycle). A minimum of 3 subjects will be treated. If 1 of 3 subjects experiences DLT during Cycle 1, the cohort will be expanded to 6. If  $\geq 2$  of 6 subjects experiences DLT by Day 28, no dose escalation to Dose Level 2 will occur. However, if 0 of 3 or  $\leq 1$  of 6 subjects treated at Dose Level 1 experiences DLT by Day 28, dose escalation will proceed to the next cohort, 320 mg/m<sup>2</sup> weekly (*Dose Level 2*), administered by IV infusion over 2 hours on Days 1, 8, 15, and 22 of a 28-day schedule. A minimum of 3 subjects will be treated at this dose level. If 1 of 3 subjects treated at Dose Level 2 experiences DLT during Cycle 1, the cohort will be expanded to 6 subjects. If  $\geq 2$  of 6

subjects experience DLT by Day 28, no further dose escalation will occur.

However, if 0 of 3 or  $\leq 1$  of 6 subjects treated at Dose Level 2 experience DLT by Day 28, dose escalation will proceed to the next dose cohort, 160 mg/m<sup>2</sup> administered as an IV infusion over 2 hours twice weekly (*Dose Level 3*), on Days 1, 4, 8, 11, 15, 18, 22 and 25 of a 28-day schedule (=1 cycle). A minimum of 3 subjects will be treated at this dose level. If 1 of 3 subjects treated at Dose Level 3 experiences DLT during Cycle 1, the cohort will be expanded to 6 subjects. If  $\geq 2$  of 6 subjects experience DLT by Day 28, no further dose escalation will occur.

However, if 0 of 3 or  $\leq 1$  of 6 subjects treated at Dose Level 3 experience DLT by Day 28, dose escalation will proceed to the next dose cohort, 240 mg/m<sup>2</sup>, administered as an IV infusion over 2 hours twice weekly (*Dose Level 4*), on Days 1, 4, 8, 11, 15, 18, 22 and 25 of a 28-day schedule. A minimum of 3 subjects will be treated at this dose level. If 1 of 3 subjects treated at Dose Level 4 experiences DLT during Cycle 1, the cohort will be expanded to 6 subjects. If  $\geq 2$  of 6 subjects experience DLT by Day 28, no further dose escalations will occur.

However, if 0 of 3 or  $\leq 1$  of 6 subjects treated at Dose Level 4 experience DLT by Day 28, dose escalation will proceed to the next dose cohort, 320 mg/m<sup>2</sup> administered as an IV infusion over 2 hours twice weekly (*Dose Level 5*), on Days 1, 4, 8, 11, 15, 18, 22 and 25 of a 28-day schedule. A minimum of 3 subjects will be treated at this dose level. If 1 of 3 subjects treated at Dose Level 5 experiences DLT during Cycle 1, the cohort will be expanded to 6 subjects. If there are  $\leq 1$  of 6 subjects with DLT at Dose Level 5, this dose (320 mg/m<sup>2</sup> twice weekly) will be declared the MTD and RP2D. If, however,  $\geq 2$  of 6 subjects experience DLT, then either 320 mg/m<sup>2</sup> weekly (Dose Level 2) or 240 mg/m<sup>2</sup> twice weekly (Dose Level 4) will be declared the MTD and RP2D based on additional factors (e.g., PK and PD parameters).

Dose-limiting toxicity will be defined as any one of the following events: prolonged myelosuppression (as defined by the National Cancer Institute [NCI] criteria specific for leukemia, i.e., marrow cellularity  $< 5\%$  at  $\geq 6$  weeks from start of therapy without evidence of leukemia);  $\geq$  Grade 3 non-hematologic toxicity (excluding Grade 3 nausea, vomiting or diarrhea that is adequately controlled with supportive care and resolves to  $\leq$  Grade 2 within 48 hours, or Grade 3 electrolyte disturbances responsive to correction within 24 hours);  $\geq$  Grade 3 liver function tests (LFTs) lasting  $> 7$  days; ; treatment interruption  $> 14$  days due to toxicity; or other important medical event.

Phase 2a (Expansion): Once the Phase 1 Safety Run-In portion of the study is complete and an RP2D is established, additional subjects will be enrolled into the Phase 2 Expansion portion in three cohorts. Cohort 1 will enroll up to 26 patients with relapsed or refractory AML and confirmed FLT3 mutation (with or without a Ras mutation) without prior exposure to a FLT3 inhibitor. Cohort 2 will enroll up to 26 patients with relapsed or refractory AML and confirmed FLT3 mutation (with or without a Ras mutation) with prior exposure to a FLT3 inhibitor. Cohort 3 will enroll up to 10 patients with relapsed or refractory AML and a confirmed Ras mutation with no FLT3 mutation. Cohorts 1 and 2 of the Expansion Phase will incorporate a Simon 2-stage optimal design.

Subjects with AML enrolled in the Phase 1 portion of the study at the RP2D will count towards the Phase 2a accrual for the appropriate cohort.

During the study, a Safety Review Committee (SRC), consisting of the actively recruiting investigators, the Medical Monitor and Strategia Therapeutics will review data from each cohort on an ongoing basis.

Subjects will receive E6201 weekly or bi-weekly on a 28-day schedule, with the schedule and dose level established in the safety run-in portion of the study. Disease assessments, including analysis of blood and bone marrow aspirates, will be performed at the end of Cycles 1 and 3 and every 2 cycles thereafter. Disease assessments may be made at other time points at the discretion of the Investigator.

Subjects who demonstrate clinical benefit (objective response or stable disease) will be allowed to continue therapy with E6201 until progression of disease, observation of unacceptable adverse events, intercurrent illness or changes in the patient's condition that prevents further study participation.

Subjects will be instructed to contact their study doctor for ophthalmologic evaluation should they experience disturbances in their vision.

ECGs will be taken within 28 days prior to Cycle 1, and Days 1 and 15 of each cycle, pre-dose, 5 minutes following the end of the infusion, 2, 4 and 24 hours post-infusion, and at the End-of-Study visit.

Blood for hematology and serum chemistry will be collected within 28 days prior to Cycle 1 Day 1, on Days 1, 8, 15 and 22 of Cycle 1, on Day 1 of each subsequent cycle and at the End-of-Study visit.

Blood samples for PK assessment of E6201 concentrations will be collected on Cycle 1 Days 1 and Day 15, and Cycle 2 Day 1 pre-dose, 5 minutes following the end of the infusion, 2, 4, 8 and 24 hours post-infusion.

Blood samples for PD assessment will be collected at Cycle 1, Days 1 and 15 and Cycle 2 Day 1, pre-dose, 4 and 24 hours post-infusion.

Bone marrow will be collected pre-study, at the end of Cycle 1, every 2 cycles thereafter, and at disease relapse/progression, unless the peripheral blood absolute blast count is  $\geq 5.1 \times 10^9$  cells/L, to assess mutational status and potentially PD markers.

Safety will be assessed through the monitoring of adverse events (AEs), clinical laboratory parameters (hematology and serum chemistry), vital sign measurements, ECGs and physical examinations. Adverse events will be classified according to the Medical Dictionary for Regulatory Affairs (MedDRA) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Efficacy assessment for AML will be performed using a modification of the recommendations of the International Working Group (IWG) for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Efficacy assessments for subjects with MDS or CMML will be performed using a modification of the IWG Response Criteria in Myelodysplasia.

Pharmacokinetic determinations of E6201 in plasma will be made.

Levels of pERK, pFLT3, pAKT, FLT3 ITD, FLT3 TKD and Ras allelic burden, FLT3 ligand and plasma inhibitory assay (PIA) for FLT3, will be measured in blood and/or bone marrow samples collected from each subject as pharmacodynamics endpoints and correlated with FLT3 and Ras+ allelic burden, pharmacokinetics and clinical response.

### **3.2. Number of Subjects and Centers**

Phase 1: Up to 30 subjects are planned for the Safety Run-in portion of the study.

Phase 2a: Up to 26 subjects are planned for Cohort 1 of the Expansion portion and 26

subjects for Cohort 2 (total N=52) and up to 10 subjects for Cohort 3. Therefore, up to 92 total subjects are planned.

The study will be conducted at The University of Texas M.D. Anderson Cancer Center with Gautam Borthakur, M.D. serving as Study Chair. Additional clinical sites include Moffitt Cancer Center (Kendra Sweet, MD), Health ONE Cares (Michael Maris, MD) and Methodist Hospital, San Antonio (Jose Cruz, MD). Additional sites may be added to complete the study in a timely manner.

### **3.3. Duration of Study**

The accrual phase for the Phase 1 safety run-in portion is expected to be 24-27 months. The expected accrual for the Phase 2a Expansion portion is expected to be 12 months, for a total accrual period of 36-39 months. With the last subject follow up for up to 6 months, a total study duration of 42-45 months is anticipated. The anticipated accrual rate is 4–6 subjects per month across all sites.

### **3.4. Criteria for Termination of the Study**

If the sponsor, investigators, study monitor or regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study site should be terminated, this action may be taken after appropriate consultation between the sponsor and investigators.

Conditions that may warrant termination include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- A decision on the part of the sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of an investigator to enroll subjects into the study at an acceptable rate
- Failure of an investigator to comply with pertinent FDA regulations
- Submission of knowingly false information from the study site to the sponsor, study monitor or the FDA
- Insufficient adherence to protocol requirements

Study termination and follow-up would be performed in compliance with the conditions set forth in 21 CFR 312.50 and 21 CFR 312.56.

## **4. STUDY POPULATION**

### **4.1. Inclusion Criteria**

Subjects must meet all of the following criteria to participate in the study:

- Males and females  $\geq 18$  years of age
- Phase 1: Subjects with confirmed relapsed or refractory AML with a documented FLT3 and/or Ras mutation, or age  $\geq 60$  years with newly diagnosed FLT3+ and/or Ras+ AML and not eligible for standard induction chemotherapy, or FLT3+ and/or Ras+ higher-risk MDS/CMML (defined as  $\geq 10\%$  marrow blasts or  $\geq 5\%$  peripheral blood blasts or Revised International Prognostic Scoring System

[IPSS-R] score<sup>16</sup>  $\geq 3.5$ ), and relapsed or refractory to prior therapy

- Phase 2: Subjects with confirmed relapsed or refractory AML with a documented FLT3 and/or Ras mutation, or age  $\geq 60$  years with newly diagnosed FLT3+ and/or Ras+ AML and not eligible for standard induction chemotherapy
- At least 3 weeks beyond the last cancer treatment for the disease under study, major surgery and recovered from all acute toxicities ( $\leq$  Grade 1) by first dose of study drug (C1D1). *Hydroxyurea used to control peripheral blast counts is permitted during the first 2 cycles.*
- Adequate performance status: Eastern Cooperative Oncology Group (ECOG)  $\leq 2$  **(Appendix A)**
- Adequate renal and hepatic function:
  - Serum creatinine  $\leq 1.5$  mg/dL OR calculated creatinine clearance  $\geq 45$  mL/minute per the Cockcroft-Gault formula **(Appendix B)**
  - Total bilirubin  $\leq 2$  times the upper limit of normal (ULN), unless due to Gilbert's disease or thought to be due to underlying AML
  - ALT and AST  $\leq 5$  times ULN
- Negative serum pregnancy test within 14 days prior to the first dose of study therapy for women of child-bearing potential (WCBP), defined as a sexually mature woman who has not undergone a hysterectomy or who has not been naturally post-menopausal for at least 24 consecutive months (i.e., who has had menses any time in the preceding 24 consecutive months). Sexually active WCBP and male subjects must agree to use adequate methods to avoid pregnancy (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study and for 28 days after the completion of study treatment.
- Ability to provide written informed consent

#### 4.2. Exclusion Criteria

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

- History of clinically significant cardiac impairment, congestive heart failure (CHF) New York Heart Association (NYHA) Class III or IV, unstable angina, or myocardial infarction during the previous 6 months, or serious cardiac arrhythmia **(Appendix C)**
- QT interval corrected for rate (QTc)  $> 450$  msec for males and  $> 460$  msec for females on the electrocardiogram (ECG) obtained at Screening using the Fridericia method for QTc calculation (average of 3 readings)
- Concomitant medication(s) that may cause QTc prolongation or induce Torsades de Pointes with the exception of anti-microbials that are used as standard of care to prevent or treat infections and other such drugs that are considered by the Investigator to be essential for the care of the patient **(Appendix D)**. However, if such medications are deemed to be necessary during the study, more intensive ECG monitoring will be added during the period of concomitant drug administration.
- Presence of active central nervous system (CNS) leukemia. Subjects adequately treated for CNS leukemia documented by 2 consecutive cerebrospinal fluid samples



negative for leukemia cells are eligible. Subjects with no history of CNS leukemia will not be required to undergo cerebrospinal fluid sampling for eligibility.

- Known positive for human immunodeficiency virus (HIV), hepatitis B virus surface antigen (HbsAg), or hepatitis C virus (HCV)
- Active, uncontrolled infection
- Known hypersensitivity to any study drug component
- Any other medical intervention or other condition which, in the opinion of the Principal Investigator, could compromise adherence to study requirements or confound the interpretation of study results
- Pregnancy or lactation

#### **4.3. Molecular Characterization of Mutational Status**

For sites with the ability to characterize the FLT3 and Ras mutational status (quantitative allelic burden) in a CLIA-certified laboratory setting, the local lab results may be used for Screening. For subjects whose mutational status is not known at the time of screening, a bone marrow or peripheral blood sample will be collected prior to enrollment. The subject may be enrolled only if mutational testing shows the presence of a FLT3 and/or Ras mutation.

#### **4.4. Discontinuation of Subjects**

##### **4.4.1. Procedures for Withdrawal**

Any subject may be removed from study for the following reasons:

- Subject withdrawal of the informed consent
- Subject noncompliance
- An increasing or unexpected pattern of unacceptable toxicity
- Disease progression or confirmed loss of clinical response
- Investigator judgment when the well-being and best interest of the subject is compromised

Subjects experiencing unacceptable toxicity should be removed from the study once complete resolution of toxicity has been documented. Individual subjects may be discontinued from the study by the investigator or sponsor at any time if either determines that it is not in the best interest of the subject to continue.

Any subject who becomes pregnant during the study must be discontinued from the study immediately, but should be followed through delivery or termination of the pregnancy. Subjects should also notify the investigator if they become pregnant within 28 days following the last dose of study drug. Strategia Therapeutics also must be notified if a subject becomes pregnant on study.

If a subject is discontinued from the study before completing the specified duration of treatment, they should be encouraged to complete the end-of-study assessments and to agree to report any serious adverse events for 28 days following the last dose of study drug. The date the subject is withdrawn and the primary reason for discontinuation will be recorded on the case report form (CRF).

#### **4.4.2. Replacement of Study Subjects**

Subjects who are screened but do not receive E6201, and subjects treated in Cycle 1 who complete < 75% of their prescribed study drug treatment or do not complete C1D28 evaluation due to progression of disease, withdrawal of consent or non-DLT adverse events, will be replaced.

### **5. STUDY TREATMENT**

#### **5.1. E6201 Study Drug Description**

E6201 for Injection is a sterile white lyophilized powder containing 60 mg of E6201 formulated in cyclodextrin to improve E6201 solubility in water.

#### **5.2. Study Drug Preparation and Administration**

E6201 will be provided directly from the Strategia Therapeutics drug distribution center.

Each vial contains 60 mg of E6201 and will be reconstituted with 8.5 mL of Sterile Water for Injection to provide a solution of E6201 at a concentration of 6 mg/mL and a pH of approximately 4.5. Once the Sterile Water is added, gently swirl to mix and let sit until totally dissolved. This may take up to 30 minutes to go into solution. Each reconstituted vial will contain 10 mL of E6201 solution.

After reconstitution, the appropriate number of vials may be combined as needed per dose calculation. The resulting solution will be diluted to 250 mL in 0.9% Sodium Chloride.

Reconstituted and diluted E6201 solutions should be stored refrigerated (2 to 8°C) and protected from light before administration. E6201 solutions can be stored under refrigerated conditions (2 to 8°C) for up to 24 hours. Light protection is not required during the 2 hour ( $\pm$  10 minutes) infusion time. However, E6201 should not be exposed to normal light for > 3 hours at room temperature.

Subjects should be scheduled to begin study therapy following completion of Screening. E6201 will be administered at the dose level prescribed per cohort by IV infusion over 2 hours ( $\pm$  10 minutes) in normal saline. Subjects will receive E6201 weekly or twice weekly on a 28-day schedule, based on the dose cohort to which they have been assigned.

In the absence of lengthy clinical experience, E6201 should be considered an irritant and precautions should be taken to avoid extravasation. With IV administration of E6201, extravasation may occur with, or without an accompanying stinging or burning sensation (even if blood returns on aspiration of the infusion needle). If any signs or symptoms of extravasation occur, the infusion should be immediately terminated and restarted in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction.

E6201 must not be given by intramuscular or subcutaneous route.

#### **5.3. Treatment Duration**

Treatment will continue until confirmation of disease progression, unacceptable toxicity, or subject decision to discontinue therapy.

## 5.4. Dosing Delays and Modifications Due to Toxicity

### 5.4.1. Toxicity Grading Criteria

Toxicity grading is based on NCI Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE v4.03); <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>.

### 5.4.2. Definitions of Dose-Limiting Toxicity

A DLT is defined as any one of the following events:

- Prolonged myelosuppression (as defined by the NCI criteria specific for leukemia, i.e., marrow cellularity < 5% at  $\geq 6$  weeks from start of therapy without evidence of leukemia)
- $\geq$  Grade 3 non-hematologic toxicity (excluding Grade 3 nausea, vomiting or diarrhea that is adequately controlled with supportive care and resolves to  $\leq$  Grade 2 within 48 hours, or Grade 3 electrolyte disturbances responsive to correction within 24 hours)
- $\geq$  Grade 3 liver function tests (LFTs) lasting > 7 days
- Treatment interruption > 14 days due to toxicity
- Other important medical event

### 5.4.3. Dose Modifications and Dose Reductions

Patients who experience a DLT may continue treatment at the next lower dose level until disease progression or unacceptable toxicity.

Adverse events considered for dose reduction should not include the events assessed by the investigator as exclusively related to underlying disease or other medical condition or concomitant treatment.

The dose modification guidelines for general adverse events are outlined in **Table 7**. Provisions are not made for dose levels below 160 mg/m<sup>2</sup>. If 160 mg/m<sup>2</sup> weekly is determined to be unsuitable based on DLT as defined above, E6201 will be permanently discontinued.

**Table 7. E6201 Dose Modification Guidelines for General Adverse Events**

Dose Modifications for Weekly Dosing Schedule		
Dose Level	Modified Dose Level -1	Modified Dose Level -2
240 mg/m <sup>2</sup> weekly	160 mg/m <sup>2</sup> weekly	-
320 mg/m <sup>2</sup> /weekly	240 mg/m <sup>2</sup> weekly	160 mg/m <sup>2</sup> /weekly
Dose Modifications for Twice Weekly Dosing Schedule		
Dose Level	Modified Dose Level -1	Modified Dose Level -2
160 mg/m <sup>2</sup> twice weekly	160 mg/m <sup>2</sup> weekly	-
240 mg/m <sup>2</sup> twice weekly	160 mg/m <sup>2</sup> twice weekly	160 mg/m <sup>2</sup> weekly
320 mg/m <sup>2</sup> twice weekly	240 mg/m <sup>2</sup> twice weekly	160 mg/m <sup>2</sup> twice weekly

Dose modifications for QTc prolongation are defined in **Table 8** below.

**Table 8. E6201 Dose Modification Guidelines for QTc Prolongation**

<b>QTc Criteria</b>	<b>E6201 Dose</b>
QTc greater than 500 msec or $\geq 60$ msec from baseline on at least 2 separate ECGs	Withhold until recovery to baseline, then resume at reduced unit dose (50%)
QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	Permanently discontinue

#### **5.4.4. Schedule Adjustments for Toxicity**

- Dosing delays are permitted for DLT and clinically-significant toxicities. Once a DLT has resolved to  $\leq$  Grade 1, the patient may resume treatment. The dose level must be reduced to the next lower dose level when treatment is re-initiated following a delay for drug-related toxicity unless otherwise specified. For a dose delay that occurs for a reason other than DLT, a dose reduction is not mandatory when resuming treatment.
- The maximum delay allowed between treatment cycles is 2 weeks. If toxicity has not resolved after 2 weeks of delay, the Medical Monitor should be contacted to discuss permission for resuming treatment after a longer delay for patients who are experiencing clinical benefit.
- There will be no dose adjustment for myelosuppression unless the myelosuppression meets the definition for DLT as described above.

#### **5.5. Supportive Care Guidelines**

- Medications may be administered for the management of symptoms associated with the administration of E6201, as required.
- Prophylactic pre-medication will not be used routinely. Adequate treatment for nausea and/or vomiting and diarrhea is permitted during Cycle 1. After Cycle 1, prophylaxis of nausea and/or vomiting and diarrhea is permitted.
- Granulocyte stimulating growth factors (e.g., G-CSF or GM-CSF) are not allowed during Cycle 1 except for the following situations (defined as DLT): any  $\geq$  Grade 3 neutropenia lasting  $\geq 6$  weeks from start of study drug, in the setting of  $< 5\%$  marrow cellularity without evidence of leukemia. After Cycle 1, use of granulocyte growth factors are allowed for prophylaxis or management of neutropenia.
- Erythropoiesis-stimulating agents, transfusions, etc. are permitted for management of hematologic toxicities.

#### **5.6. Concomitant Medications and Therapies**

##### **5.6.1. Permitted Medications**

All medications and other treatments taken by subjects 4 weeks before and throughout the study period will be recorded in the CRF module. Any changes in documented, permitted concomitant medications being taken at the beginning of the clinical trial or added during the time the patient is participating in this study (through the End of Study

Visit) must be recorded in the CRF module.

*Hydroxyurea to control peripheral blast counts is permitted during the first 2 cycles.*

If a concomitant medication that is known to prolong QTc cannot be avoided, perform an additional ECG before first dose of QTc prolongation medication, and another one upon completion of the first dose of QTc prolongation medication (oral medications, approximately 2 hours after first dose; IV medications, at end of infusion), if start of QTc prolongation medication is outside specified ECG study days.

#### **5.6.2. Prohibited Medications**

Concurrent anti-tumor therapy of any kind or any other investigational agent is prohibited.

Concomitant medication(s) that may cause QTc prolongation or induce Torsades de Pointes are prohibited, with the exception of anti-microbials that are used as standard of care to prevent or treat infections and other such drugs that are considered by the Investigator to be essential for the care of the patient. However, if such medications are deemed to be necessary during the study, more intensive ECG monitoring will be added during the period of concomitant drug administration. See **Appendix D** for a list of drugs that may cause QTc prolongation or induce Torsades de Pointes.

#### **5.7. Packaging and Labeling**

E6201 for Injection is packaged in a 15-mL or 20-mL capacity Type I glass vial with a bromobutyl rubber stopper and an aluminum cap for IV administration. The study drug vials will be labeled with strength and other information as per local regulatory requirements.

#### **5.8. Shipping and Storage**

E6201 for Injection is demonstrated to be stable when stored in the defined container closure system. E6201 for Injection should be stored refrigerated at 2 to 8 °C and protected from light.

#### **5.9. Study Drug Accountability**

The investigator must maintain accurate records of receipt of study drug, dispensing information, and the prompt return or destruction of unused supplies. A drug accountability log will be supplied to each clinical site for purposes of recording study drug dispensation for the study and will be monitored by Sponsor personnel. If the site has an electronic study drug accountability form that is in keeping with institutional practice and the form collects the same information as the form supplied by the Sponsor, this form may be substituted for the Sponsor's drug accountability form.

Unused or unexpired E6201 for Injection will be destroyed per institutional policy.

### **6. STUDY PROCEDURES**

See Schedule of Study Procedures in **Appendix E**.

#### **6.1. Screening Procedures**

The following evaluations are to be performed within 28 days of study treatment to determine subject eligibility

- Administration of informed consent

- Medical history, physical examination and vital signs
- ECOG Performance Status
- Height and weight
- The following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Beta HCG pregnancy test for WCBP
- 12-lead ECG (in triplicate)
- Collection of bone marrow for mutational analysis and PD assessment
- Review of concomitant medications

## **6.2. Requirements During Treatment Cycle 1**

### **6.2.1. Cycle 1, Day 1**

- Abbreviated physical examination
- Vital signs
- ECOG Performance Status
- Weight
- The following lab tests
  - Hematology, if not performed within previous 24 hours
  - Serum chemistry, if not performed within previous 24 hours
- Study drug administration (*also on Day 4 for subjects in twice weekly cohorts*)
- 12-lead ECG, pre-dose, at 5 minutes after the infusion ends ( $\pm 5$  minutes), and at 2, 4 ( $\pm 15$  minutes) and 24 hours ( $\pm 2$  hours) post-infusion (each reading in triplicate)
- Collection of blood samples for PK determinations pre-dose, at 5 minutes after the infusion ends ( $\pm 5$  minutes), and at 2, 4 hours ( $\pm 15$  minutes), 8 ( $\pm 1$  hour) and 24 ( $\pm 2$  hours) hours post-infusion
- Collection of blood samples for PD determinations pre-dose, 4 hours ( $\pm 15$  minutes) and 24 hours ( $\pm 2$  hours) post-infusion
- Review of concomitant medications
- Assessment of adverse events
- Assessment for survival

### **6.2.2. Cycle 1, Day 8 (+/-1 day)**

- Vital signs
- The following lab tests:
  - Hematology

- Serum Chemistry
- Study drug administration (*also on Day 11 for subjects in twice weekly cohorts*)
- Review of concomitant medications
- Assessment of adverse events
- Assessment for survival

**6.2.3. Cycle 1, Day 15 (+/-1 day)**

- Vital signs
- The following lab tests:
  - Hematology
  - Serum Chemistry
- Study drug administration (*also on Day 18 for subjects in twice weekly cohorts*)
- 12-lead ECG, pre-dose, at 5 minutes after the infusion ends ( $\pm 5$  minutes), and at 2, 4 ( $\pm 15$  minutes) and 24 hours ( $\pm 2$  hours) post-infusion (each reading in triplicate)
- Collection of blood samples for PK determinations pre-dose, at 5 minutes after the infusion ends ( $\pm 5$  minutes), and at 2, 4 hours ( $\pm 15$  minutes), 8 ( $\pm 1$  hour) and 24 hours ( $\pm 2$  hours) post-infusion
- Collection of blood samples for PD determinations pre-dose, 4 hours ( $\pm 15$  minutes) and 24 hours ( $\pm 2$  hours) post-infusion
- Review of concomitant medications
- Assessment of adverse events
- Assessment for survival

**6.2.4. Cycle 1, Day 22 (+/-1 day)**

- Vital signs
- The following lab tests:
  - Hematology
  - Serum Chemistry
- Study drug administration (*also on Day 25 for subjects in twice weekly cohorts*)
- Review of concomitant medications
- Assessment of adverse events
- Assessment for survival

**6.2.5. End of Cycle 1 (Day 28 +/- 3 days)**

- Bone marrow aspirate or biopsy for response and PD assessments, unless peripheral blood absolute blast count is  $\geq 5.0 \times 10^9$  cells/L
- Disease assessment for response

- Review of concomitant medications
- Assessment of adverse events
- Assessment for survival

### **6.3. Requirements During Treatment Cycles After Cycle 1 (Cycles 2, 3, 4, etc.)**

#### **6.3.1. Day 1 (+/- 1 day)**

- Abbreviated physical examination
- Vital signs
- ECOG Performance Status
- Weight
- The following lab tests (+/- 3 days)
  - Hematology
  - Serum chemistry
- Study drug administration (*also on Day 4 for subjects in twice weekly cohorts*)
- 12-lead ECG, pre-dose, at 5 minutes after the infusion ends ( $\pm 5$  minutes), and at 2, 4 ( $\pm 15$  minutes) and 24 hours ( $\pm 2$  hours) post-infusion (each reading in triplicate)
- Collection of blood samples for PK determinations pre-dose, at 5 minutes after the infusion ends ( $\pm 5$  minutes), and at 2, 4 ( $\pm 15$  minutes), 8 ( $\pm 1$  hour) and 24 hours ( $\pm 2$  hours) post-infusion (*Cycle 2 only*)
- Collection of blood samples for PD determinations pre-dose, 4 hours ( $\pm 15$  minutes) and 24 hours ( $\pm 2$  hours) post-infusion (*Cycle 2 only*)
- Review of concomitant medications
- Assessment of adverse events
- Assessment for survival

#### **6.3.2. Day 8 (+/-1 day)**

- Study drug administration (*also on Day 11 for subjects in twice weekly cohorts*)
- Review of concomitant medications
- Assessment of adverse events
- Assessment for survival

#### **6.3.3. Day 15 (+/-1 day)**

- 12-lead ECG, pre-dose, at 5 minutes after the infusion ends ( $\pm 5$  minutes), and at 2, 4 ( $\pm 15$  minutes) and 24 hours ( $\pm 2$  hours) post-infusion (each reading in triplicate).
- Study drug administration (*also on Day 18 for subjects in twice weekly cohorts*)
- Review of concomitant medications



- Assessment of adverse events
- Assessment for survival

**6.3.4. Day 22 (+/-1 day)**

- Study drug administration (*also on Day 25 for subjects in twice weekly cohorts*)
- Review of concomitant medications
- Assessment of adverse events
- Assessment for survival

**6.3.5. End of Cycle 3 (Day 28 +/- 3 days) and Every 2 Cycles Thereafter**

- Bone marrow aspirate or biopsy for response and PD assessments, unless peripheral blood absolute blast count is  $\geq 5.0 \times 10^9$  cells/L
- Disease assessment for response
- Review of concomitant medications
- Assessment of adverse events
- Assessment for survival

**6.4. At Relapse or Progression of Disease**

- Bone marrow aspirate or biopsy for response status and PD assessment, unless peripheral blood absolute blast count is  $\geq 5.0 \times 10^9$  cells/L
- Disease assessment for response
- Review of concomitant medications
- Assessment of adverse events
- Assessment for survival

**6.5. End of Study (28 Days After Last Dose of Study Medication +/- 5 days)**

- Physical examination
- Vital signs
- ECOG Performance Status
- Weight
- The following lab tests
  - Hematology
  - Serum chemistry
- 12-lead ECG (in triplicate)
- Review of concomitant medications
- Assessment of adverse events
- Assessment for survival

## 6.6. Long-Term Follow-Up

Long-term follow-up will consist of a clinic visit or telephone call to assess survival every 3 months for up to 6 months.

## 7. DESCRIPTION OF ASSESSMENTS

### 7.1 Safety Assessments

#### 7.1.1. Adverse Event Definition

An adverse event (AE) includes any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as indicated by physical signs, symptoms, and/or laboratory changes occurring whether or not temporally associated with study drug administration and whether or not considered related to study drug. This definition includes an exacerbation of pre-existing medical conditions or events, intercurrent illnesses, hypersensitivity reactions, drug interactions, or clinically significant laboratory findings.

An AE does **not** include the following:

- Medical or surgical procedures, e.g., tooth extraction, transfusion, surgery (The medical condition that leads to the procedure is to be recorded as an AE.)
- Pre-existing conditions or procedures present or detected at the start of the study that do not worsen
- Hospitalization for elective surgeries or for other situations in which an untoward medical event has not occurred
- Abnormal laboratory value, unless it is clinically significant
- Overdose of study drug or concomitant medication unaccompanied by signs/symptoms (If sign/symptoms occur, the final diagnosis should be recorded as an AE.)
- Pregnancy by itself, unless a complication occurs during pregnancy leading to hospitalization; in this case (The medical condition that leads to the hospitalization is to be recorded as the AE.)
- A significant worsening of the disease under investigation which is captured as an efficacy parameter in this study and, thus, is not to be recorded as an AE.

#### 7.1.2. Serious Adverse Event

A serious adverse event (SAE) is defined as an adverse event that results in any of the following outcomes:

- Death
- Life-threatening, i.e., immediate risk of death from the event as it occurred; (This does not include an adverse event that, had it occurred in a more serious form, might have caused death.)
- Persistent or substantial disability/incapacitation
- Results in or prolongs an existing inpatient hospitalization

- 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 on medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

#### **7.1.3. Unexpected Adverse Event**

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, is not consistent with the risk information described in the protocol or elsewhere. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the investigational therapy, but are not specifically mentioned as occurring with the investigational therapy.

#### **7.1.4. Adverse Event Reporting Period**

The adverse event reporting period begins from the date of the first dose of study drug to 28 days following the last dose of study drug.

#### **7.1.5. Recording of Adverse Events**

Each AE should be recorded in standard medical terminology on the AE CRF module. Whenever possible, the AE should be evaluated and reported as a diagnosis rather than as individual signs or symptoms. For example, cough, runny nose, sneezing, sore throat, and head congestion should be reported as 'upper respiratory infection'. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded. Dates of start (onset) and stop (recovery), action taken, and outcome will be recorded in the AE CRF module.

All clinically significant abnormal changes in laboratory parameters will be recorded as an AE on the AE module, with the following exceptions: clinically significant abnormal laboratory changes determined to be related to the study condition and concomitant conditions, e.g., diabetes, of which the investigator was previously aware and that have not worsened.

The investigator will evaluate all AEs with regard to maximum intensity and relationship to study drug, as follows.

##### **7.1.5.1. Maximum Intensity**

Maximum intensity should be assigned using one of the severity grades as outlined in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03); if the AE is not specifically listed in CTCAE v4.03, use the following grades:

- Grade 1: mild

- Grade 2: moderate
- Grade 3: severe
- Grade 4: life-threatening or disabling
- Grade 5: death

#### **7.1.5.2. Relationship to Study Drug**

The degree of certainty with which an AE is attributed to study drug (or alternative causes, e.g., natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of known pharmacology of the study drug and/or reactions of similar nature previously observed with study drug. Each AE will be assigned one of the following five categories:

- *Not related:* There is not a temporal relationship to the study drug (e.g., too early, too late), or there is a reasonable causal relationship to another drug, concurrent illness, or circumstance.
- *Unlikely related:* There is a temporal relationship to study drug, but there is not a reasonable causal relationship between the time of study drug administration and the AE (i.e., it is doubtful the AE is related to the study drug); could be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment.
- *Possibly related:* There is a reasonable temporal sequence from time of study drug administration (e.g., occurred in a time frame relevant to study drug dose); or for which the possibility of the study drug being the causative factor (e.g., existence of similar reports attributed to the study drug; reactions attributable to the pharmacological effect) could not be excluded, although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable.
- *Probably related:* There is a reasonable temporal sequence from time of study drug administration; and for which the possibility of factors other than the study drug administration, such as underlying disease, complications, concomitant drugs, or concurrent treatment, could not be excluded as the cause.
- *Definitely related:* Follows a clear temporal sequence from time of study drug administration; could not be possibly explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; follows a response pattern known to be associated with study drug administration.

#### **7.1.6. Adverse Event Reporting**

Each AE is to be reported by the investigator as serious or non-serious according to the definitions above. This classification determines the regulatory reporting procedures to be followed as described in **Table 9**.

**Table 9. Reporting Guidelines for Adverse Events**

<b>Gravity of AE</b>	<b>Reporting Time to Strategia Therapeutics</b>	<b>Type of Report</b>
Serious	Within 24 hours after the site becomes aware of the event	Initial SAE Report
Non-Serious	Per AE CRF module	Completed AE CRF Module

Any SAE, regardless of relationship to investigational therapy that occurs within 28 days following the last dose of study drug must be reported to the Medical Monitor within 24 hours after the site becomes aware of the event. The investigator is encouraged to discuss with the Medical Monitor any adverse experiences for which the issue of reportability is unclear or questioned. The initial report should be followed by submission of a more detailed SAE Report when follow-up information is available.

If the SAE occurs more than 28 days after the last dose of study drug, SAEs should be reported **only if considered related to E6201**. In the event of subject death, the reason for death should be recorded as the SAE, with 'death' recorded as the outcome on the SAE CRF module.

The SAE also will be recorded as an AE on the AE CRF module. Note: the SAE Report is different from the AE CRF. In areas of both forms where the same data are reported, the forms will be completed in a consistent manner. For example, the same term should be used for the AE on both forms, with the same start and stop dates, action taken, outcome, etc. A checkbox on the AE CRF module for whether the AE resulted in an SAE, will link the two types of report for a given event.

An SAE Report should be prepared with as much available information concerning the event as possible so that a written report can be filed with the appropriate regulatory authorities. If causality cannot be determined definitively at the time of the SAE occurrence, it is important to notify Strategia Therapeutics within the timeline stated above, and to attribute the relationship as 'Not Assessable' (only applicable for the initial SAE Report). When new significant information is obtained and the outcome and attribution of the event is known, the investigator will communicate this in a follow-up SAE Report. This relevant information will be provided in a timely manner to allow reporting to regulatory authorities within the required reporting period. Any SAE follow-up information requested by Strategia Therapeutics, Inc. should be provided in a timely manner.

As necessary, the SAE Report should be accompanied by relevant pages from the CRFs, e.g., medical history, AEs, concomitant medications. Additional information may be requested by Strategia Therapeutics in an expedited manner to ensure that the initial reporting of the SAE made to the regulatory authorities complies with the required time frame. Strategia Therapeutics may be required to collect and report additional information to the regulatory authorities in a follow-up report, containing a final evaluation of the event, including copies of hospital reports, autopsy reports, or other relevant information.

#### **7.1.7. Adverse Event and Serious Adverse Event Follow-Up**

All AEs and SAEs should be followed until resolution, return to baseline, or until the point it is deemed that further recovery is unlikely. All measures required for AE management and the ultimate outcome of the AE will be recorded in the source document and AE CRF

module.

#### **7.1.8. Ongoing Safety Evaluation**

A study safety evaluation will be conducted on a regular (monthly) basis by teleconference. Dose exposure, dose-limiting toxicity, AE/SAE profiles and clinical laboratory abnormalities, and other safety measures will be reviewed during each convened meeting. Subject accrual will not be interrupted during the regular scheduled safety evaluations. These discussions will be led by the Strategia Therapeutics Medical Monitor and Principal Investigator.

#### **7.1.9. Clinical Laboratory Tests**

Clinical laboratory tests include hematology, serum chemistry and bone marrow assessment (**Table 10**).

**Table 10. Clinical Laboratory Parameters**

<b>Hematology</b>	<b>Serum Chemistry</b>	<b>Bone Marrow Aspirate/Biopsy</b>
Red blood cell count	Serum creatinine	Marrow blast percent
Hemoglobin	BUN	Marrow cellularity percent
Hematocrit	Glucose (non-fasting)	Cell line maturation
White blood cell count	Albumin	Auer rods
Differential:	AST	Dysplasia
Neutrophils	ALT	Cytogenetic abnormalities
ANC	LDH	
Lymphocytes	Total bilirubin	
Monocytes	Total protein	
Eosinophils	Alkaline phosphatase	
Basophils	Calcium	
Platelets	Phosphorus	
Blasts percent	Magnesium	
	Sodium	
	Potassium	
	Chloride	
	Bicarbonate	

#### **7.1.10. Vital Sign Measurements**

Vital sign measurements include temperature, blood pressure and pulse rate. Additional measurements may be obtained if clinically indicated. Any value considered clinically significant by the investigator will be recorded as an AE on the CRF. Clinically significant changes compared to baseline values should be followed until clinical resolution.

#### **7.1.11. Physical Examinations**

Complete physical examinations include the following body system evaluations: General Appearance, Skin, Musculo-skeletal, Eyes, Ears, Nose, Throat, Cardiovascular, Chest, Abdomen, Lymph Nodes, and Neurological. Symptom-oriented (abbreviated) evaluations will be performed at study visits where indicated, and otherwise when clinically indicated.

Weight will be measured at Screening, Day 1 of each treatment cycle, and the End of Study Visit.

### **7.1.12. Electrocardiograms**

12-lead ECGs will be performed at Screening, Days 1 and 15 of each cycle (pre-dose, 5 minutes after end of infusion, and 2, 4 and 24 hours post-infusion) and at End of Study (in triplicate).

## **7.2. Efficacy Assessments**

### **7.2.1. Criteria for Evaluation of Response and Progression**

Evaluation of response to treatment and determination of disease progression in patients with AML will be evaluated using criteria defined in Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia.<sup>17</sup> Efficacy assessments for subjects with MDS or CMML will be made using the modified International Working Group Response Criteria in Myelodysplasia.<sup>18</sup>

### **7.2.2. Disease Response Criteria**

#### **7.2.2.1. Subjects with AML**

- **Complete Remission (CR)**

The subject must be free of all symptoms related to leukemia and have an absolute neutrophil count  $> 1.0 \times 10^9/L$ , platelet count  $\geq 100 \times 10^9/L$ , and normal bone marrow with  $< 5\%$  blasts and no Auer rods

- **Complete Remission with Incomplete Blood Count Recovery (CRi)**

As per CR but with residual thrombocytopenia (platelet count  $< 100 \times 10^9/L$ ) or residual neutropenia (absolute neutrophil count  $< 1.0 \times 10^9/L$ )

- **Partial Remission (PR)**

A  $\geq 50\%$  decrease in bone marrow blasts to 5 to 25% abnormal cells in the marrow; or CR with  $\leq 5\%$  blasts if Auer rods are present

- **Treatment Failure**

Treatment has failed to achieve CR, CRi, or PR.

- **Recurrence**

Relapse after confirmed CR: reappearance of leukemic blasts in peripheral blood or  $\geq 5\%$  blasts in the bone marrow not attributable, in the Investigator's opinion, to any other cause (e.g., bone marrow regeneration after consolidation therapy), or appearance of new dysplastic changes.

#### **7.2.2.2. Subjects with High-Risk MDS or CMML**

- **Complete Remission (CR)**

The subject must be free of all symptoms related to leukemia and have an absolute neutrophil count  $\geq 1.0 \times 10^9/L$ , platelet count  $\geq 100 \times 10^9/L$ , bone marrow  $\leq 5\%$  myeloblasts, with normal maturation of all cell lines, hemoglobin  $\geq 11g/dL$ , and no blasts in the peripheral blood

- **Partial Remission (PR)**

All CR criteria with  $\geq 50\%$  decrease in bone marrow blasts over pre-treatment (but still  $> 5\%$ )

- **Marrow CR**

In bone marrow,  $\leq 5\%$  myeloblasts and decrease by  $\geq 50\%$  over pre- treatment

- **Hematologic Improvement (HI)**

- **Erythroid Response (HI-E)**

- **Major Response**

- ◇ For subjects with pretreatment hemoglobin  $< 11$  g/dL,  $> 2$  g/dL increase in hemoglobin

- ◇ For RBC transfusion-dependent subjects, transfusion independence

- **Minor Response**

- ◇ For subjects with pretreatment hemoglobin  $< 11$  g/dL, 1 to 2 g/dL increase in hemoglobin

- ◇ For RBC transfusion-dependent subjects,  $\geq 50\%$  decrease in transfusion requirements

- **Platelet Response (HI-P)**

- **Major Response**

- ◇ For subjects with a pretreatment platelet count  $< 100 \times 10^9/L$ , an absolute increase of  $\geq 30 \times 10^9/L$

- ◇ For platelet transfusion-dependent subjects, stabilization of platelet transfusion independence

- **Minor Response**

- ◇ For subjects with a pretreatment platelet count  $< 100 \times 10^9/L$ , a  $\geq 50\%$  increase in platelet count with a net increase  $> 10 \times 10^9/L$  but  $< 30 \times 10^9/L$

- **Neutrophil Response (HI-N)**

- **Major Response**

- ◇ For absolute neutrophil count (ANC)  $< 1.5 \times 10^9/L$  before therapy,  $\geq 100\%$  increase or an absolute increase of  $\geq 0.5 \times 10^9/L$ , whichever is greater

- **Minor Response**

- ◇ For ANC  $< 1.5 \times 10^9/L$  before therapy, ANC  $\geq 100\%$ , but absolute increase  $< 0.5 \times 10^9/L$

- **Progressive Disease**

Subject did not achieve PR, CR or marrow CR or is otherwise a non-responder.

- **Relapse after CR or PR**

One or more of the following:



- Return to pretreatment bone marrow blast percentage
- Decrement of  $\geq 50\%$  from maximum remission/response levels in granulocytes or platelets
- Reduction in hemoglobin concentration by  $\geq 2$  g/dL or transfusion dependence.

- **Progression or Relapse after Hematologic Improvement**

One or more of the following:

- A  $\geq 50\%$  decrement from maximum response levels in granulocytes or platelets
- A reduction in hemoglobin concentration by  $\geq 2$  g/dL
- Transfusion

### **7.2.3. Efficacy Endpoints**

#### **7.2.3.1. Primary Efficacy Endpoint**

To evaluate the proportion of subjects with objective response achieved within 3 cycles of treatment with E6201 in patients with relapsed/refractory AML and FLT3 and/or Ras mutation without or with prior exposure to a FLT3 inhibitor (Phase 2: Cohorts 1 and 2, respectively), or with a Ras mutation and no FLT3 mutation (Phase 2: Cohort 3), or in subjects with FLT3+ and/or Ras+ high-risk MDS or CMML.

- **Subjects with AML**

Objective responses for subjects with AML include complete remission (CR), complete remission with incomplete blood count recovery (CRi) and partial remission (PR), as defined above.

- **Subjects with MDS**

Objective responses for subjects with MDS include CR, PR and marrow CR, as defined above.

- **Subjects with CMML**

Objective responses for subjects with CMML include CR, PR and marrow CR, as defined above.

#### **7.2.3.2. Secondary Efficacy Endpoints**

To evaluate duration of response, progression-free survival and overall survival, as defined below:

- **Duration of Response:** length of time from the first evidence of objective response (CR, CRi, PR) to the first objective evidence of progression
- **Progression-Free Survival:** length of time from the date of first administration of study drug to the first objective evidence of disease progression or death, whichever is earlier
- **Overall Survival:** length of time from the date of first administration of study drug to the date of death from any cause.

### 7.2.3.3. Timing of Assessments to Determine Objective Response

Disease assessments will be made at the end of Cycles 1 and Cycle 3, and every 2 cycles thereafter. Disease assessments may be made at other time points at the discretion of the Investigator.

### 7.2.4. Pharmacokinetic Endpoints

Mean plasma concentrations of E6201 will be determined in blood samples collected before administration of E6201 and at multiple time points after administration of E6201. Because plasma concentrations will be determined at a limited number of time points during the study, a complete pharmacokinetic profile of E6201 at each dose level will not be possible. Limited pharmacokinetic analyses will be performed.

### 7.2.5. Pharmacodynamic Endpoints

Levels of pERK, pFLT3, pAKT, FLT3 ITD allelic burden, FLT3 ligand and plasma PIA for FLT3 will be measured in blood and/or bone marrow samples collected from each subject at multiple points during the study. pERK and pFLT3 will be measured in bulk and progenitor cells. Correlation between FLT3 ITD allelic burden, pharmacokinetics and clinical response will be assessed. Additional markers, or other genomic changes, may be evaluated.

Changes from baseline in PD parameters for each cohort will be summarized using descriptive statistics, including number of patients (N), mean, standard deviation (SD), minimum, median, maximum range, and coefficient of variation (CV).

## 8. STATISTICAL METHODOLOGY

### 8.1. Determination of Sample Size

Phase 1: The sample size reflects requirements associated with a 3+3 design. A total of 3 to 30 subjects are planned (3 to 6 subjects in each of 5 dose cohorts) with FLT3+ and/or Ras+ AML, MDS or CMML.

Phase 2a, Cohort 1: The statistical objective for Cohort 1 in the dose expansion portion of the study is evaluation of the objective response (OR) rate within 3 cycles of treatment with E6201 in patients with AML and FLT3 mutation, or FLT3 plus Ras mutations, without prior exposure to a FLT3 inhibitor. We are testing  $H_0$ : true OR rate  $\leq 5\%$  versus  $H_1$ : true OR rate  $\geq 25\%$ . An objective response rate (OR) of 25% or greater is deemed clinically important. An OR of less than or equal to 5% is not clinically valuable. Rejecting the null hypothesis, which rules out the OR rate of less than or equal to 5%, demonstrates that the study drug is efficacious and warrants further testing. The null hypothesis (true OR rate  $\leq 5\%$ ) will be tested with the alternative hypothesis (true OR  $\geq 25\%$ ). Based on Simon's 2-stage optimal design, eight (8) patients will be enrolled in Stage I. If there are zero (0) ORs in these 8 patients, the cohort will be terminated. If there is at least 1 OR in the first 8 patients, 18 additional patients will be enrolled in Stage II, for a total of 26 evaluable patients. If there are at least 4 ORs in a total of  $N=26$ , the alternative hypothesis will be accepted. This design provides a type I error of 5% and power of 85% when the true OR rate is 25%.

Phase 2a, Cohort 2: The statistical objective for Cohort 2 in the dose expansion portion of the study is evaluation of the objective response (OR) rate within 3 cycles of treatment with E6201 in patients with AML and FLT3 mutation, or FLT3 plus Ras mutations, with prior

exposure to a FLT3 inhibitor. We are testing  $H_0$ : true OR rate = 0% versus  $H_1$ : true OR rate  $\geq 15\%$ . An objective response rate (OR) of 15% or greater is deemed clinically important. An OR of equal to 0% is not clinically valuable. Rejecting the null hypothesis, which rules out the OR rate of less than or equal to 0%, demonstrates that the study drug is efficacious and warrants further testing. The null hypothesis (true OR rate = 0%) will be tested with the alternative hypothesis (true OR  $\geq 15\%$ ). Based on Simon's 2-stage optimal design, eleven (11) patients will be enrolled in Stage I. If there are zero (0) ORs in these 11 patients, the cohort will be terminated. If there is at least 1 OR in the first 11 patients, 15 additional patients will be enrolled in Stage II, for a total of 26 patients. If there are at least 2 ORs in a total of  $N=26$ , the alternative hypothesis will be accepted. This design provides a type I error of 5% and power of 80% when the true OR rate is 15% or greater.

Phase 2a, Cohort 3: We will evaluate the objective response (OR) rate within 3 cycles of treatment with E6201 in up to 10 patients with AML and Ras mutation but no mutation in FLT3. A response rate of 20% in this patient population is considered clinically meaningful.

## **8.2. Analysis Populations**

The full analysis set (FAS) includes all subjects who are administered any fraction of a dose of study medication. For a particular measure, the per-protocol set (PPS) includes those subjects in the FAS who have had a valid baseline and one or more post-treatment assessments for that measure of interest.

The E6201 PK population consists of all subjects in the FAS who complete all PK assessments.

The E6201 PD population consists of all subjects in the FAS who complete all PD assessments.

## **8.3. Statistical Analysis Methods**

All data will be analyzed using Statistical Analysis System (SAS Version 9.3 or higher for Windows, SAS Institute, Cary, NC). Continuous variables will be summarized using number, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using number and frequencies.

### **8.3.1. Safety Analyses**

#### **8.3.1.1. Adverse Events**

All safety endpoints will be summarized using descriptive statistics and will be based on the FAS dataset.

All AEs will be coded based on the Medical Dictionary for Regulatory Affairs (MedDRA; Version 15.0 or higher). An AE will be considered a treatment emergent adverse event (TEAE) if the onset is after the first dose of study drug or if the condition was present at baseline but worsened after the first dose.

All AEs for each subject will be listed, including intensity grading, relationship to study drug, action taken and outcome. Subject listings of deaths, SAEs, and AEs leading to treatment discontinuation will be provided. Subject narratives will be provided for deaths, SAEs and other significant AEs. Summary tables will be prepared to examine TEAE severity and relationship to study treatment.

AE summaries will be produced separately for each dose cohort and overall, and each disease cohort by dose and overall. All summaries will show, by subject group, dose

cohort and overall, the number and percentage of subjects experiencing at least 1 TEAE of each preferred term, arranged by system organ class, and the number of occurrences of the event. Separate summaries will be produced by relationship to study medication, by severity, and for those events with an incidence rate of at least 2% in any group or overall.

SAEs will be summarized in a similar manner; overall, by relationship to study medication, and by severity.

In addition to the above, summaries of the number and percentage of subjects discontinuing the study due to AEs and, due to death, will be presented.

#### **8.3.1.2. Laboratory Data**

Laboratory data will be listed by subject. Values above and below normal ranges will be indicated, and whether statistically significant. All laboratory values will be graded according to the NCI-CTCAE version 4.03 criteria. Laboratory data will be summarized by actual value and change from baseline using number of non-missing observations, mean standard deviation, median, minimum and maximum. In addition, shift tables and the incidence of Grade 3 or 4 laboratory values will be presented.

#### **8.3.1.3. Vital Signs**

Vital signs will be listed by subject. Values above and below normal ranges will be indicated as will clinical significance. Vital sign data will be summarized by actual value and change from baseline using number of non-missing observations, mean, standard deviation, median, minimum and maximum.

#### **8.3.1.4. Other Safety Data**

Data collected for physical examinations, ECGs and related measures will be listed.

### **8.3.2. Efficacy Analyses**

#### **8.3.2.1. Primary Efficacy Endpoint**

The primary endpoint is the proportion of patients treated at the RP2D who achieve an objective response (OR) within 3 cycles of treatment with E6201 (i.e., within 3 months). The proportion of subjects in each disease cohort treated at the RP2D will be summarized, and 90% confidence intervals will be provided.

#### **8.3.2.2. Secondary Efficacy Endpoints**

For secondary endpoints, duration of response, progression-free survival and overall survival curves will be estimated at the RP2D using the Kaplan-Meier product-limit estimates. Median and 90% confidence intervals of time-to-event will be estimated. Duration of response will be calculated from the time of first evidence of response (CR, CRi, PR) to the first objective evidence of disease progression. Progression-free survival will be calculated from the date of first dose of study drug to the date of first objective evidence of disease progression or death, whichever is earlier. Overall survival will be calculated from the date of first dose of study drug to the date of death due to any cause. Subjects who did not experience progression or death will be censored at the last follow-up time point.

### **8.3.3. Pharmacokinetic Endpoint Analysis**

Mean plasma concentrations of E6201 will be determined at each time point for evaluation of dose-linearity. Because a limited number of plasma concentrations will be determined, full determination of routine pharmacokinetic parameters may not be possible. In addition

to mean plasma concentrations, as the data allow, additional pharmacokinetic analyses will be provided (trough levels,  $t_{1/2}$ ,  $T_{max}$ ,  $C_{max}$ , AUC, etc.)

#### **8.3.4. Pharmacodynamic Endpoint Analysis**

Changes from baseline in levels of pERK, pFLT3, pAKT, FLT3 ITD, FLT3 TKD and Ras allelic burden, FLT3 ligand and PIA for FLT3 will be measured in blood and/or bone marrow samples collected from each subject. Correlation between FLT3 and Ras allelic burden and clinical response will be assessed. Pharmacodynamic parameters will be summarized using descriptive statistics including the number of subjects, mean, standard deviation, minimum, median, maximum, range, and coefficient of variation.

Any additional biomarkers collected or genomic changes evaluated will be summarized accordingly.

### **9. STUDY MANAGEMENT**

#### **9.1. Data Management**

The investigator is responsible for completing and maintaining adequate and accurate source documentation. Source documentation constitutes original records, which may include: progress notes, medication administration records, laboratory reports, ECG tracings, discharge summaries, CRF worksheets, etc. Data for this study will be submitted electronically. Access to the database will be provided following a brief on-line training session. Each user will receive a unique username and password, which should not be shared. The investigator must sign the investigator's statement for each subject indicating that the data reported are accurate. See **Appendix F** for Ethical Standards to be followed during the study.

#### **9.2. Monitoring**

Strategia Therapeutics is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the sponsor's study monitors will contact the study site via visits to the site, telephone calls, and letters in order to review study progress, CRF completion and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of subjects, subject recruitment, subject compliance with the study procedures, source data verification, drug accountability, use of concomitant therapy by subjects, AE and SAE documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

#### **9.3. Audits and Inspections**

Strategia Therapeutics, a regulatory authority or an IRB may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact Strategia Therapeutics immediately if contacted by a regulatory agency about an inspection at their site.

#### **9.4. Amendments**

Any amendments to the protocol will be prepared by Strategia Therapeutics. All amendments must be submitted to the prevailing IRB for approval prior to implementing the changes at each institution. In some instances, an amendment requires changes to the informed consent form, which also must be submitted for IRB approval prior to administration to subjects. If any changes to the CRFs are required, Strategia Therapeutics will issue supplemental or revised CRF pages.

#### **9.5. Record Keeping**

##### **9.5.1. Health Insurance Portability Accountability Act of 1996**

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR. Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the sponsor. See **Appendix G** for Investigator Obligations.

##### **9.5.2. Financial Disclosure**

The investigator shall provide to Strategia Therapeutics sufficient accurate financial information to allow Strategia Therapeutics to submit complete and accurate financial certification or disclosure statements to the FDA. The investigator shall promptly update this information if any relevant changes occur in the course of the study or for one year following completion of the study.

##### **9.5.3. Access to Original Records**

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation to ensure data integrity. "Original" in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

##### **9.5.4. Retention of Study Documents**

Study-related records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor.

The investigator must not destroy any study-related records without receiving approval from the sponsor. The investigator must notify the sponsor in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor must be contacted to arrange alternative record storage options.

#### **10. ADMINISTRATIVE STRUCTURE OF THE STUDY**

Strategia Therapeutics will be responsible for data management, statistical analyses, and clinical study report writing. Clinical monitors under the direction of Strategia

Therapeutics will be used to monitor the study. Clinical laboratory parameters will be assessed by local laboratories and results recorded in the CRF module.

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**Appendix A. Eastern Cooperative Group (ECOG) Performance Status Scale**

<b>ECOG PERFORMANCE STATUS*</b>	
<b>Grade</b>	<b>ECOG</b>
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

\* From ECOG, Robert Comis, MD, Group Chair

*Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

**Appendix B. Cockcroft-Gault Formula for Calculation of Creatinine Clearance**

Creatinine clearance must either be measured or estimated using the Cockcroft-Gault formula, as outlined below.

$$\begin{aligned} \text{Creatinine clearance (mL/min)} = & \\ & \frac{(140 - \text{age [years]}) \times \text{weight [kg]}}{\text{serum creatinine } [\mu\text{mol/L}]} \quad (\text{Females}) \\ & \frac{(140 - \text{age [years]}) \times \text{weight [kg]} \times 1.2}{\text{serum creatinine } [\mu\text{mol/L}]} \quad (\text{Males}) \end{aligned}$$

**Appendix C. New York Heart Association (NYHA) Classification for Heart Failure NYHA  
Classification - The Stages of Heart Failure**

<b>Class</b>	<b>Patient Symptoms</b>
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

**Appendix D. Drugs Known to Prolong QT Interval or Induce Torsades de Pointes****CredibleMeds Known QTDrug List**

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic	Abnormal heart rhythm
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor	Thrombocythemia
Arsenic trioxide	Trisenox	Anticancer	Cancer (leukemia)
Astemizole (Removed from Market)	Hismanal	Antihistamine	Allergic rhinitis
Azithromycin	Zithromax, Zmax	Antibiotic	Bacterial infection
Bepridil (Removed from Market)	Vascor	Antianginal	Angina Pectoris (heart pain)
Chloroquine	Aralen	Antimalarial	Malaria
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic	Schizophrenia, nausea, many others
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor	Intermittent claudication
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic	Bacterial infection
Cisapride (Removed from Market)	Propulsid	GI stimulant	Increase GI motility
Citalopram	Celexa, Cipramil	Antidepressant, SSRI	Depression
Clarithromycin	Biaxin, Prevpac	Antibiotic	Bacterial infection
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)
Disopyramide	Norpace	Antiarrhythmic	Abnormal heart rhythm
Dofetilide	Tikosyn	Antiarrhythmic	Abnormal heart rhythm
Domperidone (Only on Non US Market)	Motilium, Motillium, Motinorm Costi, Nomit	Antinausea	Nausea, vomiting
Donepezil	Aricept	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Dronedarone	Multaq	Antiarrhythmic	Abnormal heart rhythm
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocin, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Zineryt, Abbotcin, Abbotcin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic	Bacterial infection, increase GI motility
Escitalopram	Ciprallex, Lexapro, Nexito, Anxiset-E (India), Exodus (Brazil), Esto (Israel), Seroplex, Elicea, Lexamil, Lexam, Entact (Greece), Losita (Bangladesh), Reposil (Chile), Animaxen (Colombia), Esitalo (Australia), Lexamil (South Africa)	Antidepressant, SSRI	Depression (major), anxiety disorders
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic	Abnormal heart rhythm
Fluconazole	Diflucan, Trican	Antifungal	Fungal infection
Gatifloxacin (Removed from Market)	Tequin	Antibiotic	Bacterial infection
Grepafloxacin (Removed from Market)	Raxar	Antibiotic	Bacterial infection
Halofantrine	Halfan	Antimalarial	Malaria
Haloperidol	Haldol (US & UK), Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol (Germany), Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic	Schizophrenia, agitation

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Ibutilide	Corvert	Antiarrhythmic	Abnormal heart rhythm
Levofloxacin	Levaquin, Tavanic	Antibiotic	Bacterial infection
Levomepromazine (Only on Non US Market)	Nosinan, Nozinan, Levoprome	Antipsychotic	Schizophrenia
Levomethadyl acetate (Removed from Market)	Orlaam	Opioid agonist	Narcotic dependence
Levosulpiride (Only on Non US Market)	Lesuride, Levazeo, Enliva (with rabeprazole)	Antipsychotic	Schizophrenia
Mesoridazine (Removed from Market)	Serentil	Antipsychotic	Schizophrenia
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist	Narcotic dependence, pain
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic	Bacterial infection
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic	Nausea, vomiting
Oxaliplatin	Eloxatin	Antineoplastic Agent	Cancer
Papaverine HCl (Intra-coronary)	none	Vasodilator, Coronary	Diagnostic adjunct
Pentamidine	Pentam	Antifungal	Fungal infection (Pneumocystis pneumonia)
Pimozide	Orap	Antipsychotic	Tourette's Disorder
Probucol (Removed from Market)	Lorelco	Antilipemic	Hypercholesterolemia
Procainamide	Pronestyl, Procan	Antiarrhythmic	Abnormal heart rhythm
Propofol	Diprivan, Propoven	Anesthetic, general	Anesthesia
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic	Abnormal heart rhythm

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Roxithromycin (Only on Non US Market)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycin, Roxomycin, Rulid, Tirabycin, Coroxin	Antibiotic	Bacterial infection
Sevoflurane	Ulane, Sojourn	Anesthetic, general	Anesthesia
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic	Abnormal heart rhythm
Sparfloxacin (Removed from Market)	Zagam	Antibiotic	Bacterial infection
Sulpiride (Only on Non US Market)	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical	Schizophrenia
Sultopride (Only on Non US Market)	Barnetil, Barnotil, Topral	Antipsychotic, atypical	Schizophrenia
Terfenadine (Removed from Market)	Seldane	Antihistamine	Allergic rhinitis
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic	Schizophrenia
Vandetanib	Caprelsa	Anticancer	Cancer (thyroid)



## Appendix E. Schedule of Study Procedures

Study Activity	Screening <sup>a</sup>	Treatment Cycle 1					Treatment Cycles after Cycle 1					Progression or Relapse	End of Study <sup>o</sup>	Long-Term Follow-Up <sup>p</sup>
		Day 1	Day 8 <sup>i</sup>	Day 15 <sup>i</sup>	Day 22 <sup>i</sup>	End of Cycle 1 <sup>m</sup>	Day 1 <sup>i</sup>	Day 8 <sup>i</sup>	Day 15 <sup>i</sup>	Day 22 <sup>i</sup>	End of Cycle 3 <sup>m,n</sup>			
Signed ICD	X													
Medical history	X													
Physical examination	X	X <sup>k</sup>					X <sup>k</sup>						X	
Vital Signs	X	X	X	X	X		X						X	
ECOG Performance Status	X	X					X						X	
Height	X													
Weight	X	X					X						X	
Hematology <sup>b</sup>	X	X	X	X	X		X						X	
Serum chemistry <sup>c</sup>	X	X	X	X	X		X						X	
Beta-hCG for WCBP	X													
12-lead ECG <sup>d</sup>	X	X		X			X		X				X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event assessment		X	X	X	X	X	X	X	X	X	X	X	X	
Bone Marrow Aspirate/biopsy <sup>e</sup>	X					X					X	X		
Disease Assessment <sup>f</sup>						X					X	X		
Peripheral blood for PK assessment <sup>g</sup>		X		X			C2 Only							
Peripheral blood for PD assessment <sup>h</sup>		X		X			C2 Only							
Bone marrow for PD assessment <sup>i</sup>	X					X					X	X		
Administration of E6201 <sup>j</sup>		X	X	X	X		X	X	X	X				
Assessment of survival		X	X	X	X	X	X	X	X	X	X	X	X	X

- <sup>a</sup> Screening to be performed within 28 days of Cycle 1, Day 1
- <sup>b</sup> Hematology collected at Screening, Cycle 1 Day 1 (only if not performed within the previous 24 hours), Days 8, 15 and 22, Day 1 of each subsequent cycle (within 3 days of Day 1 of each subsequent cycle) and End of Study. See **Table 9** for tests to be conducted at each time point.
- <sup>c</sup> Serum chemistry collected at Screening, Cycle 1 Day 1 (only if not performed within the previous 24 hours), Days 8, 15 and 22, Day 1 of each subsequent cycle (within 3 days of Day 1 of each subsequent cycle) and End of Study. See **Table 9** for tests to be conducted at each time point.
- <sup>d</sup> ECGs performed in triplicate every cycle Day 1 and 15: pre-dose, 5 minutes after end of infusion ( $\pm 5$  minutes), and 2, 4 ( $\pm 15$  minutes) and 24 hours ( $\pm 2$  hours) post-infusion. If on a concomitant medication known to prolong QTc, perform an additional ECG before first dose of QTc prolongation medication, and another one upon completion of the first dose of QTc prolongation medication (oral medications, approximately 2 hours after first dose; IV medications, at end of infusion), if start of QTc prolongation medication is outside specified ECG study days
- <sup>e</sup> Bone marrow aspirate/biopsy required at Screening; at end of Cycles 1 and 3, every 2 cycles thereafter, and at relapse/progression, unless peripheral blood absolute blast count is  $\geq 5.0 \times 10^9$  cells/L. See **Table 9** for tests to be conducted at each time point.
- <sup>f</sup> Disease Assessment may include bone marrow assessment, hematology for blood counts, physical exams, etc.
- <sup>g</sup> Peripheral blood collected for PK assessment at Cycle 1, Day 1, Day 15 and Cycle 2 Day 1: pre-dose, 5 minutes after end of infusion ( $\pm 5$  minutes), and 2, 4 hours ( $\pm 15$  minutes), 8 hours ( $\pm 1$  hour) and 24 hours ( $\pm 2$  hours) post-infusion.
- <sup>h</sup> Peripheral blood collected for PD assessment at Cycle 1, Day 1, Day 15 and Cycle 2 Day 1: pre-dose, 4 hours ( $\pm 15$  minutes) and 24 hours ( $\pm 2$  hours) post-infusion.
- <sup>i</sup> Best effort should be made to collect bone marrow (aspirate or biopsy) for PD assessment at this visit. May be omitted if it would require a separate bone marrow collection procedure beyond that necessary for disease assessment and patient has a peripheral blood absolute blast count  $\geq 5.0 \times 10^9$  cells/L.
- <sup>j</sup> Dose weekly IV over a 2 hour ( $\pm 10$  minutes) infusion Day 1, 8, 15 and 22 each 28-day cycle, **or twice weekly Day 1, 4, 8, 11, 15, 18, 22, 25 each 28-day cycle**, based on assigned dose cohort
- <sup>k</sup> Abbreviated physical exam
- <sup>l</sup> Day 1, 8, 15, or 22  $\pm 1$  day. All visit procedures must be conducted on the scheduled visit day. Pre-dose procedures must be conducted prior to receipt of study drug dose.
- <sup>m</sup> Day 28  $\pm 3$  days
- <sup>n</sup> And every 2 cycles thereafter
- <sup>o</sup> End of Study visit should be 28 days from last dose of study medication ( $\pm 5$  days)
- <sup>p</sup> Long-term follow-up for 6 months consists of clinic visits or telephone calls every 3 months to assess survival status

## Appendix F. Ethical Standards

### Ethics and Regulatory Considerations

This study will be conducted according to Good Clinical Practice (GCP), US 21 Code of Federal Regulations (CFR) Part 50, (Protection of Human Subjects), US 21 CFR Part 56 (Institutional Review Boards), International Conference on Harmonisation Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance, the Nuremberg Code, and the Declaration of Helsinki.

### General Instructions

The U.S. Food and Drug Administration (FDA) regulates studies of drugs, biologics, and medical devices. Consequently, these studies are subject to GCP and FDA regulations and guidance issued by the FDA and are included in, but not limited to, the following parts of the CFR and guideline document:

- 21 CFR Part 11 – Electronic Records; electronic signatures
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 312 – Investigational New Drug Application
- FDA Guidance for Industry: Oversight of Clinical Investigations —A Risk-Based Approach to Monitoring, August 2013
- FDA Guidance for IRBs, Clinical Investigators, and Sponsors, June 2010
- FDA Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects, October 2009
- FDA Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE studies, December 2012
- Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, 1996

Copies of these materials are available from the sponsor upon request. The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- Human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- The study is conducted with diligence and in conformance with the protocol in such a way as to insure the integrity of the findings;
- The potential benefits of the research justify the risks.

Strategia Therapeutics, Inc. is the Sponsor of the IND. The Sponsor is responsible for the following:

- Selecting qualified investigators,
- Providing investigators with the information they need to properly conduct an

investigation,

- Ensuring proper monitoring of the investigation,
- Ensuring that the study is conducted according to the general investigational plan and protocols contained in the IND,
- Maintaining the IND, and
- Ensuring that FDA and all participating investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied.

### **Appendix G. Investigator Obligations**

Per Title 21 of the US Government Code of Federal Regulations (21 CFR) Parts 50 and 56, the study protocol and the final version of the subject informed consent form will be approved by the institutional review board (IRB) before enrollment of any subjects. The opinion of the IRB will be dated and given in writing. A copy of the letter of approval from the IRB and a copy of the approved informed consent form will be received by the sponsor prior to shipment of study medication supplies to the investigator.

The investigator will ensure that the IRB will be promptly informed of all changes in the research activity and of all unanticipated problems including risk to subjects. The investigator will also ensure that no changes will be made to the protocol without IRB approval.

As a part of the IRB requirement for continuing review of approved research, the investigator will be responsible for submitting periodic progress reports to the IRB at intervals appropriate to the degree of subject risk involved, but no less than once per year.

Written informed consent must be given freely and obtained from every subject prior to clinical trial participation. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

As described in GCP guidelines and FDA regulations, study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). A FDA Form 1572 will be collected, listing the principal investigator and sub-investigators involved in the study. Study personnel will not include individuals against whom sanctions have been invoked after scientific misconduct or fraud (e.g., loss of medical licensure, debarment). Quality assurance systems and procedures will be implemented to assure the quality of every aspect of the study.

#### **Protection of Human Subjects (21 CFR Part 50)**

Informed consent must be obtained from every subject before entry into a clinical study. It must be given freely and not under duress. Consent must be documented by use of an IRB-approved consent form and signed by the subject or the subject's legally authorized representative. The Department of Health and Human Services suggests that when minors are involved, a parent or guardian should sign the consent form. If the minor is an adolescent, his signature should also be included. Non-English-speaking subjects must be presented with a consent form written in a language that they understand. A copy of the signed consent form must be given to the subject signing it. Another copy must be kept in the investigator's files and made available to and FDA representatives upon request. If, for any reason, subject risk is increased as the study progresses, a revised, IRB-approved consent form must be signed by the subject. Before the study begins, a sample of the consent form must be provided to the sponsor for review. The FDA may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all subjects.

Only in the case of a life-threatening incident may an investigational product be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB within 5 working days. In this situation, the investigator may not administer any subsequent product to that subject until informed consent and IRB approval are obtained.

#### ***Informed Consent***

Written informed consent must be obtained from each subject prior to entry in the study. One copy of the signed informed consent document will be given to the subject, and another will

be retained by the investigator. Additionally, the participant must be allowed adequate time to consider the potential risks and benefits associated with his/her participation in the study. The signed and dated consent must be retained with the study records and a copy provided to each participant.

In situations where the participant is not legally competent to provide consent (i.e., mentally incapacitated), written consent must be obtained from a parent, legal guardian, or legal representative. In these situations, the consent must be signed and dated by a witness.

The informed consent document must have been reviewed and approved by the sponsor and by the investigator's IRB prior to the initiation of the study. The document must contain the eight basic elements of informed consent and may contain the six additional elements described in 21 CFR Part 50. The attached Declaration of Helsinki-provides further details regarding the specific requirements for informed consent. Every consent form must include the following eight elements:

- A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others that may reasonably be expected from the research
- A disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the subject
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility that the FDA and representatives may inspect the records
- An explanation as to whether any compensation or medical treatments are available if injury occurs for research involving more than minimal risk. The explanation should involve a description of the compensation or treatment available, or a statement describing where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and the subject's rights and whom to contact in the event of a research-related injury
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

#### *Additional Elements of Informed Consent*

When appropriate, one or more of the following elements of information shall also be included in the consent form:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable
- Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent

- Any additional costs the subject may incur from participation in the research
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject
- The approximate number of subjects involved in the study

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states, such as California and Oregon, require further action on the investigator's part concerning subject consent.

### **Institutional Review Board (IRB) Ethic Review Committee (ERC) Review/Approval**

The protocol and informed consent for this study, including advertisements used to recruit participants, must be reviewed and approved by an appropriate IRB/ERC prior to enrollment of participants in the study. It is the responsibility of the investigator to assure that all aspects of the ethical review are conducted in accordance with the current Declaration of Helsinki, International Conference on Harmonization (ICH) Good Clinical Practices, and/or local laws, whichever provide the greatest level of protection. A letter documenting the IRB/ERC approval which specifically identifies the study/protocol and a list of the committee members must be received by the sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

A progress report with a request for re-evaluation and re-approval will be submitted by the investigator to the IRB/ERC at intervals required by the IRB/ERC, and not less than annually. A copy of the report will be sent to the sponsor.

When the sponsor provides the investigator with a Safety Report, the investigator must promptly forward a copy to the IRB/ERC.

After completion or termination of the study, the investigator will submit a final report to the IRB/ERC and to the sponsor, if required. This report should include: deviations from the protocol, the number and types of participants evaluated, the number of participants who discontinued (with reasons), results of the study, if known, and significant AEs, including deaths

### **Study Files**

The investigator is required to maintain complete and accurate study documentation in compliance with current Good Clinical Practice standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study.

### **Patient Confidentiality**

The anonymity of participating subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on CRFs and other documents submitted to the clinical monitor. Documents that will be submitted to the clinical monitor and that identify the subject (e.g., the signed informed consent document) must be maintained in strict confidence by the principal investigator, except to the extent necessary to allow auditing by the FDA, the clinical monitor, or sponsor personnel.

**Investigational Product Accountability**

The investigator or designee is responsible for accountability of the investigational product at the site. The investigator or designee must maintain records of the product's delivery to the site, inventory at the site, use by each subject, and return to the sponsor or alternative disposition of any unused product. These records must include dates, quantities, batch/serial/lot numbers, and expiration dates (if applicable).

The investigator should ensure that the investigational product is used only in accordance with the protocol.