Protocol Number: KB-ENTO-3001

Official Title: A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Entospletinib in Combination with Intensive Induction and Consolidation Chemotherapy in Adults with Newly Diagnosed Nucleophosmin 1-mutated Acute Myeloid Leukemia

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Title Page

Protocol Title:

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Entospletinib in Combination With Intensive Induction and Consolidation Chemotherapy in Adults With Newly Diagnosed *Nucleophosmin 1*-mutated Acute Myeloid Leukemia

Protocol Number: KB-ENTO-3001

Version Number: 4.0 Global (Amendment 3.0 Global)

Compound: Entospletinib (ENTO, formerly known as GS-9973)

Brief Title: Entospletinib Plus Intensive Induction/Consolidation Chemotherapy in Newly Diagnosed *NPM1*-mutated AML

Study Phase: 3

Sponsor Name: Kronos Bio, Inc.

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Regulatory Agency Identifier Number(s):

IND: 116416

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FINAL PROTOCOL APPROVAL SHEET

Protocol title: **A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Entospletinib in Combination with Intensive Induction and Consolidation Chemotherapy in Adults with Newly Diagnosed *Nucleophosmin 1*-mutated Acute Myeloid Leukemia**

Sponsor: Kronos Bio, Inc.

Sponsor signatory:

[redacted]

Chief Medical Officer

[redacted]

Date

SIGNATURE OF INVESTIGATOR

Protocol title: **A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Entospletinib in Combination with Intensive Induction and Consolidation Chemotherapy in Adults with Newly Diagnosed *Nucleophosmin 1*-mutated Acute Myeloid Leukemia**

Protocol identifier: KB-ENTO-3001

This protocol is a confidential communication of Kronos Bio, Inc. (Kronos Bio). I confirm that I have read this protocol, understand it, and will execute the trial according to all of its specifications. I will also adhere consistently to the ethical principles originating in the Declaration of Helsinki and that are consistent with good clinical practices and applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval of Kronos Bio.

I have read this protocol in its entirety and agree to conduct the study accordingly.

Signature of investigator and Date: _____

Printed name of investigator: _____

Investigator title: _____

Name and address of study site: _____

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1.0 Synopsis

Protocol Title:

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of Entospletinib in Combination with Intensive Induction and Consolidation Chemotherapy in Adults with Newly Diagnosed *Nucleophosmin 1*-mutated Acute Myeloid Leukemia

Rationale:

Given the role of spleen tyrosine kinase (SYK) signaling in *HOXA9/MEIS1*-driven leukemic cell proliferation, the association between *NPM1* mutation and *HOXA9/MEIS1* dysregulation, and the preliminary promising results in early phase studies, the Sponsor will evaluate the efficacy and safety of entospletinib (ENTO) in combination with intensive induction and consolidation chemotherapy in previously untreated acute myeloid leukemia (AML) patients with mutations in *NPM1* (*NPM1*-m).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of ENTO compared to placebo when added to chemotherapy in previously untreated *NPM1*-m AML, as defined by the rate of molecularly defined measurable residual disease (MRD).	• MRD negative complete response (CR) rates after completion of 2 cycles of chemotherapy plus either ENTO or placebo. *Note:* MRD negative CR requires CR as defined by the European Leukemia Network (ELN) 2017 criteria (with minor modification for neutrophil and platelet count thresholds as defined by the International Working Group [IWG]) as assessed by study site investigators, and MRD negativity (<0.01%) in bone marrow as measured by a molecular *NPM1*-m assay (eg, next generation sequencing) in a central laboratory upon recovery of peripheral blood counts following completion of 2 cycles of chemotherapy (ie, no later than Day 42 of Cycle 2).
Secondary	
• To evaluate the efficacy of ENTO compared to placebo when added to chemotherapy in previously untreated *NPM1*-m AML, as defined by relapse-free, event-free, and overall survival.	• Event-free survival, defined as the time from randomization to the earliest occurrence of induction treatment failure, relapse from CR, or death from any cause. *Note:* Induction treatment failure is failure to achieve morphological CR after completion of

	the last cycle of induction chemotherapy (no later than Day 42 of the last cycle of induction). • Relapse-free survival, defined as the time from CR until relapse or death from any cause as assessed by study site investigators. • Overall survival defined as the time from randomization until death from any cause.
• To evaluate the efficacy of ENTO compared to placebo when added to chemotherapy in previously untreated *NPM1*-m as defined by CR rate.	• CR rates after 2 cycles of chemotherapy, as defined by ELN 2017 criteria (with minor modification for neutrophil and platelet count thresholds as defined by the IWG) as assessed by study site investigators.
• To evaluate the safety of ENTO compared to placebo when added to intensive chemotherapy.	• Type, incidence, severity, and outcome of adverse events; changes from baseline in safety laboratory assessments, ECGs, ECHO/MUGA scans, ECOG PS.
Exploratory	
• To explore the predictive value of potential biomarkers that correlate with differential outcomes (CR, MRD negativity, event-free and overall survival) among ENTO- vs placebo-treated subjects.	• Baseline expression levels of *HOXA9/MEIS1* and other relevant genes in leukemic cells from peripheral blood and bone marrow aspirate using standard expression profiling platforms (eg, Nanostring® or next-generation sequencing) for correlations with response and progression. • Mutational profiling in leukemic cells using standard platforms like next generation sequencing for correlations with response and progression. • Targeted protein/phosphoprotein profiling (eg, pSYK expression) in leukemic cells at baseline for correlations with response and progression. • Extent of ENTO target engagement as measured by pSYK expression/expression of other relevant genes for correlation with response and progression. • Level of concordance for MRD for *NPM1*-m in leukemic cells derived from bone marrow aspirate and peripheral blood. • Log reduction in *NPM1*-m alleles in bone marrow post-induction compared with baseline for correlation with response and progression.
• To assess the value of MRD detection as a prognosticator of relapse.	• Longitudinal assessment of peripheral blood for detection of *NPM1*-m alleles among subjects who achieve MRD-negative CR post-Chemotherapy Cycle 2 using standard molecular platforms (eg, next-generation

	sequencing) for correlation with morphologic relapse.
• To further assess the pharmacokinetics (PK) of ENTO in combination with intensive induction therapy for population PK modeling. • To explore the relationship between CYP2C9 genetic polymorphisms and ENTO exposure. • To assess the relationship (if any) between cytidine deaminase polymorphisms and safety and efficacy outcomes.	• Population-based PK parameter assessment. • Identification of CYP2C9 polymorphisms and population-based PK analysis. • Correlation between cytidine deaminase polymorphisms and selected safety metrics and efficacy outcomes, described above.
• To compare changes in quality-of-life measures over time among subjects treated with ENTO compared to placebo when added to intensive induction therapy in previously untreated *NPM1*-m AML.	• EQ-5D-5L and EORTC-QLQ 30 over time.

Overall Design:

This will be a multi-center, international, double-blind, placebo-controlled study in previously untreated subjects with AML harboring *NPM1* mutations. Upon fulfillment of all eligibility criteria, subjects will be randomized 1:1 to receive intensive chemotherapy in combination with either the SYK inhibitor, ENTO, or placebo. Randomization will be stratified by age (< 60 vs ≥ 60 years) and anthracycline administered during induction (daunorubicin vs idarubicin). The study will consist of Screening, Induction, Consolidation, End-of-Treatment, and Long-term Follow-up phases.

Subjects will undergo a screening bone marrow aspiration within 14 days prior to Cycle 1, Day 1 (C1D1) of induction for confirmation of diagnosis, morphology assessment (spicule prep), detection of cytogenetic abnormalities by cytogenetics/fluorescence in situ hybridization (FISH), and biomarker assessments (including *NPM1* and *FLT3* mutation status). In cases in which an adequate bone marrow aspirate cannot be obtained at Screening (eg, due to dry tap, hypocellularity or hemodilution), a trephine bone marrow biopsy is mandated.

ENTO (400 mg) or placebo will be administered continuously BID beginning on C1D1 of induction chemotherapy (Synopsis Table 1) through completion of consolidation (Synopsis Table 2), including while awaiting blood count recovery.

Synopsis Table 1: Induction Chemotherapy

	Age < 60 years	Age ≥ 60 years
Cycle 1:		
Cytarabine[a]	100 mg/m^2 by continuous infusion, Days 1-7	100 mg/m^2 by continuous infusion, Days 1-7
Anthracycline	Daunorubicin, 60 mg/m^2 slow IV push, Days 1-3 ***OR*** Idarubicin, 12 mg/m^2 slow IV push, Days 1-3	Daunorubicin, 60 mg/m^2 slow IV push, Days 1-3 ***OR*** Idarubicin, 12 mg/m^2 slow IV push, Days 1-3
Cycle 2 (if administered):		
Cytarabine	1.0 g/m^2, BID Days 1-6	1.0 g/m^2, BID Days 1-6
Anthracycline	Daunorubicin, 60 mg/m^2 slow IV push, Days 1-3 ***OR*** Idarubicin, 12 mg/m^2 slow IV push, Days 1-3	N/A

Abbreviations: BID, twice daily; IV, intravenous; N/A, not administered.

[a] Subjects who are candidates for continuous infusion of cytarabine in Cycle 1 at doses higher than 100 mg/m^2/day are ineligible.

Subjects will undergo bone marrow examination no later than Day 42 of Induction Cycle 1 for assessment of response. Subjects with ≥5% residual leukemic blasts in bone marrow will receive Induction Cycle 2 as outlined in Synopsis Table 1, which may be administered prior to blood count recovery. Subjects with <5% residual blasts will receive Consolidation Cycle 1 as outlined in Synopsis Table 2 upon recovery of peripheral blood counts (absolute neutrophil count [ANC] > 1.0 x 10^9/L; platelet count > 100 x 10^9/L). After completion of Induction Cycle 2 or Consolidation Cycle 1 (hereafter referred to collectively as Chemotherapy Cycle 2), subjects will undergo bone marrow examination for assessment of remission status at the investigative site (bone marrow biopsy is mandated if sufficient or adequate aspirate cannot be obtained, eg, due to dry tap, hemodilution or hypocellularity). Bone marrow examination should await recovery of ANC to > 1.0 x 10^9/L and platelet count to > 100 x 10^9/L later than Day 42 of Chemotherapy Cycle 2, unless leukemic progression is suspected. Subjects who achieve or remain in morphologic CR after Chemotherapy Cycle 2 will undergo MRD assessment in peripheral blood and bone marrow aspirate in a central laboratory designated by the Sponsor. Subjects who have not achieved morphologic CR after the last cycle of induction (whether it be Induction Cycle 1 or Induction Cycle 2) will be deemed treatment failures. Figure 4 provides a schematic representation of the study treatment plan from Cycle 1, Day 1 through completion of Chemotherapy Cycle 2.

Subjects who achieve MRD negative CR status post-induction will undergo retrospective MRD assessments in peripheral blood every 3 months until morphologic relapse.

All subjects who achieve morphologic CR, CRh, or CRi upon completion of Chemotherapy Cycle 2 may initiate or continue consolidation therapy in combination with ENTO or placebo (in

accordance with their original randomized treatment assignment), as outlined in Synopsis Table 2 at the investigator's discretion either instead of or as a bridge to hematopoietic stem cell transplant.

Synopsis Table 2: Treatment Phase –Consolidation

	Age < 60 years	Age ≥ 60 years
Cytarabine	3.0 g/m^2, BID over 3 hours on Days 1, 3 and 5 every 28-35 days for up to 3 cycles*	1.5 g/m^2, BID over 3 hours on Days 1, 3 and 5 every 28-35 days for up to 3 cycles*

For subjects with < 5% residual blasts post-Induction Cycle 1, Consolidation Cycle 1 will consist of Chemotherapy Cycle 2. For patients with ≥5% residual blasts post-Induction Cycle 1, Induction Cycle 2 will consist of Chemotherapy Cycle 2 (Synopsis Table 1) with consolidation beginning thereafter. All subjects are eligible to receive up to 3 cycles of high dose cytarabine after Chemotherapy Cycle 2.

All subjects will undergo an End-of-Study Treatment Visit 30 ± 7 days after the last study treatment (either ENTO/placebo or chemotherapy, whichever is later) or prior to initiation of follow-on therapy (eg, maintenance therapy, HSCT), if sooner than 30 ± 7 days after last study treatment.

All subjects regardless of their post-remission status will be followed monthly for 3 months after the End-of-Study Treatment Visit and thereafter at least once every 3 months for progression/relapse, first salvage therapy, and survival until study termination. Unscheduled study visits at other time points are permitted in the setting of suspected leukemic recurrence or for evaluation and management of post-treatment sequelae.

Number of Participants:

Approximately 180 subjects will be randomized. A sample size of 90 subjects per group will provide > 97% power to detect a difference in the MRD negative CR rate of 28% (87% CR rate x 80% MRD negativity among patients who achieve CR) = 70% for ENTO vs 70% x 60%, respectively = 42% for placebo) with a 2-sided alpha level of 0.05 (PASS 2008: Two sample test of Proportion Module). Up to 10% over enrollment is allowed in order to account for technical or logistical barriers (eg. inadequate bone marrow aspirate or poor sample quality) related to the ascertainment of MRD status in patients who achieve CR post-Chemotherapy Cycle 2.

Study Duration:

The study will be completed when all enrolled subjects either relapse, die, or after the last subject enrolled completes 5 years of follow-up, whichever is earliest.

Statistical Analysis:

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP).

Summary statistics will be used to analyze the study data. Continuous variables will be summarized by means, standard deviations, medians, quartiles, minimum and maximum values. Categorical variables will be summarized by number and percentage. Any statistical testing will be conducted at the alpha = 0.05 level (2-sided).

Unless otherwise specified, data summaries and analyses described below will be reported by treatment group.

The primary efficacy endpoint is the proportion of subjects who achieve CR without MRD (MRD negative [<0.01%] CR rate) as defined by the absence of *NPM1*-m alleles in bone marrow aspirate based on a molecular assay (eg, next generation sequencing) in a central reference laboratory designated by the Sponsor. The primary efficacy endpoint will be analyzed using the estimand as described in Section 9.4.2.1. Additional information on the handling of missing data and planned sensitivity measures will be detailed in the SAP. Risk difference will be estimated using stratum-adjusted Mantel-Haenszel proportions, and 95% confidence intervals around the treatment differences will be calculated. The differences are weighted by the harmonic mean of the sample size in each treatment group per stratum (age < 60 vs ≥ 60 years; daunorubicin vs idarubicin anthracycline).

Event-free survival (EFS) is defined as time from randomization to the earliest occurring date of induction treatment failure (ITF), relapse for those who achieve CR, or death from any cause. For this definition, ITF is failure to achieve morphological CR after completion of the last cycle of induction chemotherapy (no later than Day 42 of the last cycle of induction).

Subjects who do not experience an event (ITF, relapse from CR, or death) will be censored at their last study evaluation at which they were relapse free. Event-free survival will be estimated using the method of Kaplan-Meier and summarized by treatment group. Differences between the treatment groups will be assessed with the log rank test stratified by age (<60 vs ≥60 years) and choice of anthracycline in induction (daunorubicin vs idarubicin). Overall survival will be analyzed in a similar manner.

An independent Data Monitoring Committee (DMC), consisting of two expert hematologists, and one expert biostatistician, will monitor emerging safety and efficacy data from this trial on an ongoing basis. The DMC will provide a suitable recommendation to the Sponsor for appropriate study direction. Such direction may include continuation of the trial as planned, modification of study conduct/design or early termination for safety or futility. A DMC charter delineates the responsibilities of the DMC and its interactions with other trial components. Data monitoring committee analyses will be focused on safety and efficacy endpoints and will be conducted regularly as outlined in the DMC charter.

2.0 Introduction

2.1 Acute Myeloid Leukemia - Diagnosis, Classification, Prognosis, and Treatment in the Frontline Setting

Acute Myeloid Leukemia (AML) is an aggressive malignancy arising from hematopoietic progenitors in the bone marrow (Löwenberg 1999) and is the most common acute leukemia in adults, accounting for approximately 80% of cases. Clonal neoplastic myeloid progenitors proliferate in the bone marrow and in some cases, in extramedullary sites, causing failure of normal hematopoiesis and leading to cytopenias. Most patients diagnosed with AML present with symptoms related to bone marrow failure including fatigue, headaches, or shortness of breath from anemia, excessive or unexplained bleeding or bruising due to thrombocytopenia, or infections related to neutropenia. The categories of adult AML defined by the World Health Organization (WHO) include AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, therapy-related myeloid neoplasms, AML not otherwise specified, and myeloid sarcoma (Arber 2016).

Important prognostic factors in AML include clinical variables (age, performance status, comorbidities, antecedent history of myelodysplastic or myeloproliferative disorder, or prior treatment with DNA damaging chemotherapy), as well as cytogenetic and molecular features. The European Leukemia Network (ELN) classifies recurring cytogenetic abnormalities and mutations as conferring favorable, intermediate, or adverse risk (Döhner 2017) based on their prognostic implications. Genetic alterations not only represent independent prognostic markers, but also may constitute targets for specific therapeutic intervention. The percentage of patients in each risk category and their 5-year overall survival (OS), based on a retrospective analysis of 1116 newly diagnosed AML patients treated with intensive induction chemotherapy (Herold 2020), are shown in Table 1. According to this analysis, approximately one-third of patients < 60 years of age in the favorable risk category will die of their disease within 5 years. Although this is a substantially superior outcome compared to patients in the intermediate or adverse risk categories, it highlights an urgent need for more effective therapies for AML including among favorable risk patients.

Table 1: ELN Classification of Genetic Abnormalities and Mutations by Risk Categories and Corresponding Five-year Survival Estimates

Risk Category	Genetic Abnormality	% of Patients		5 Year OS (%)[a]	
		Age < 60	Age ≥ 60	Age < 60	Age ≥ 60
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*; Mutated *NPM1* without *FLT3-ITD* or with *FLT3-ITD*$_{low}$; biallelic mutated *CEBPA*	41.3	27.7	64	37
Intermediate	Mutated *NPM1* and *FLT3-ITD*$_{high}$; wild-type *NPM1* without *FLT3-ITD* or with *FLT3-ITD*$_{low}$ (without adverse-risk genetic lesions); t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*; cytogenetic abnormalities not classified as favorable or adverse	27.6	21.0	42	16
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*; t(v;11q23.3); *KMT2A* rearranged; t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM*(*EVI1*);-5 or del(5q); -7; -17/abn(17p); complex karyotype, monosomal karyotype; wild-type *NPM1* and FLT3-ITD$_{high}$; Mutated *RUNX1*; Mutated *ASXL1*; Mutated *TP53*	31.1	51.3	20	6

Abbreviations: ELN, The European Leukemia Network; ITD, internal tandem duplication; OS, overall survival.

[a] *Source*: Herold 2020

Frontline treatment for newly diagnosed AML is based on the age and fitness of subjects, or the presence or absence of comorbidities, and generally includes a remission induction phase, followed by a consolidation phase. Standard induction chemotherapy for subjects < 60 years old and older fit subjects typically involves 1 cycle of cytarabine administered by continuous infusion over 7 days plus 3 consecutive days of an anthracycline, such as daunorubicin or idarubicin (7 + 3). In the US, subjects with residual leukemia post-induction Cycle 1 generally receive a second induction cycle consisting of cytarabine (either by bolus or continuous infusion) with or without additional anthracycline. Elsewhere, "double induction" (ie, 2 cycles of induction for all subjects without regard for remission status post-induction Cycle 1) is generally the norm. The goal of induction is to achieve a complete response (CR), defined as fewer than 5% blasts in the bone marrow and recovery of normal hematopoiesis. CR rates after intensive induction chemotherapy

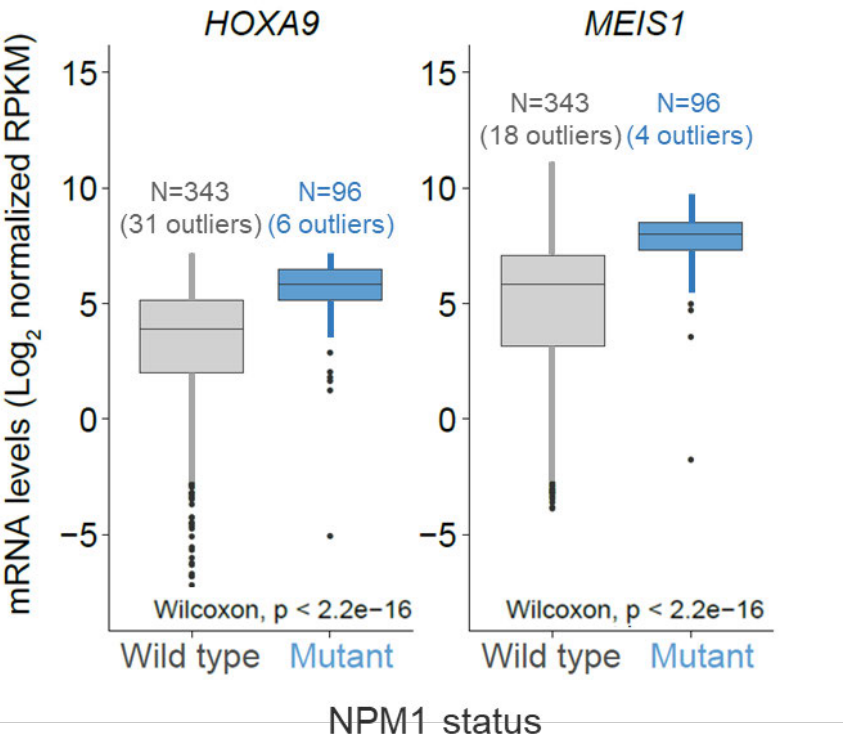
generally range from 40 to 60% in older adults (≥ 60 years of age); rates as high as 80% have been reported in younger subjects with favorable prognostic features (Döhner 2017). Subjects who fail to achieve a CR have a very grim prognosis with a 4-year survival of 23% (Othus 2015). For subjects who achieve CR, the standard of care typically includes consolidation chemotherapy, generally consisting of age-adjusted, intermediate, or high dose cytarabine, with or without additional anthracycline, or allogeneic hematopoietic stem cell transplantation (HSCT) if a suitable donor is available.

Elderly subjects (> 75 years of age) or younger subjects with comorbidities are generally not considered candidates for intensive induction and consolidation due to high risk of treatment-related morbidity and mortality. Therapeutic options for these subjects have historically been limited to low dose cytarabine with an associated CR rate of 13% and median overall survival (OS) of 4.9 months, or hypomethylating agents such as 5-azacytidine (AZA) or 5-aza-2-deoxycytidine (DAC) with a 25% to 30% CR rate and median OS less than one year (Walter 2015). The outlook for older AML patients has improved with the recent approval of the BCL-2 inhibitor, VENCLEXTA (venetoclax), and the inhibitor of the smoothened transmembrane protein, DAURISMO (glasdegib). The combination of venetoclax and AZA resulted in a composite CR rate of 66.4% and a median OS of 14.7 months and is rapidly becoming the standard of care for newly diagnosed, elderly or unfit AML patients (DiNardo 2020). DAURISMO when added to low dose cytarabine led to a CR rate of 18% and median OS of 8.3 months (DAURISMO US prescribing information).

***NPM1*-mutated AML: Effects on Expression of *HOXA9/MEIS1* Transcription Factors**

The *nucleophosmin-1* (*NPM1*) gene encodes a protein that shuttles between the nucleus and the cytoplasm, and plays a key role in histone chaperoning, centrosome duplication, and ribosome biogenesis. Mutations in *NPM1* cause a reading frame shift that creates an aberrant cytoplasmic localization signal peptide at its carboxyl terminus (Falini 2020). These are founder mutations in the leukemogenic pathway, detected exclusively in the leukemic clone and not in normal progenitors or mature hematopoietic precursors, and nearly always retained at the time of relapse. Cytoplasmic *NPM1* sequesters the myeloid lineage master transcription factor PU.1 away from the nucleus, resulting in transcriptional repression of granulocyte and monocyte differentiation programs (Gu 2018). One of the consequences of cytoplasmic *NPM1* is the persistent epigenetic activation of the genes for the homeodomain-containing transcription factors, *HOXA9* and *MEIS1* via their super enhancers (Brunetti 2018). *HOXA9 and MEIS1* function together to drive a gene expression program that defines primitive myeloid progenitors (Collins and Hess 2016). As these progenitors differentiate into mature myeloid cells, the expression of *HOXA9* and *MEIS1* is normally downregulated. Through a variety of mechanisms, this downregulation fails to occur in subjects with *NPM1*-mutated AML. As a consequence, *NPM1* mutations are associated with consistently high expression levels of *HOXA9* and *MEIS1* (Tyner 2018; Figure 1) resulting in perpetuation of the primitive myeloid progenitor phenotype. Reports have demonstrated that the overexpression of *HOXA9/MEIS1* is an adverse prognostic marker in AML (Gao 2016; Zangenberg 2009).

Figure 1: Expression of *HOXA9* and *MEIS1* mRNA in Bone Marrow Blasts From AML Patients With *NPM1* Mutations vs Wild-Type *NPM1*



Abbreviations: AML, acute myeloid leukemia; mRNA, messenger RNA; *NPM1*, *Nucleophosmin* 1; RPKM, reads per kilobase mapped.
Gene expression data from Tyner 2018. *NPM1* mutations (blue box and whiskers) vs wild-type *NPM1* (gray box and whiskers).

High *HOXA9*/*MEIS1* Expression Creates a Dependence on Spleen Tyrosine Kinase

Spleen tyrosine kinase (SYK), a nonreceptor tyrosine kinase expressed in hematopoietic cells, is involved in cellular proliferation, differentiation, and survival (Ruzza 2009). The loss of SYK expression in AML cell lines is associated with differentiation and expression of mature myeloid cell surface markers, suggesting that SYK plays a role in counteracting the differentiation of leukemic cells (Hahn 2009).

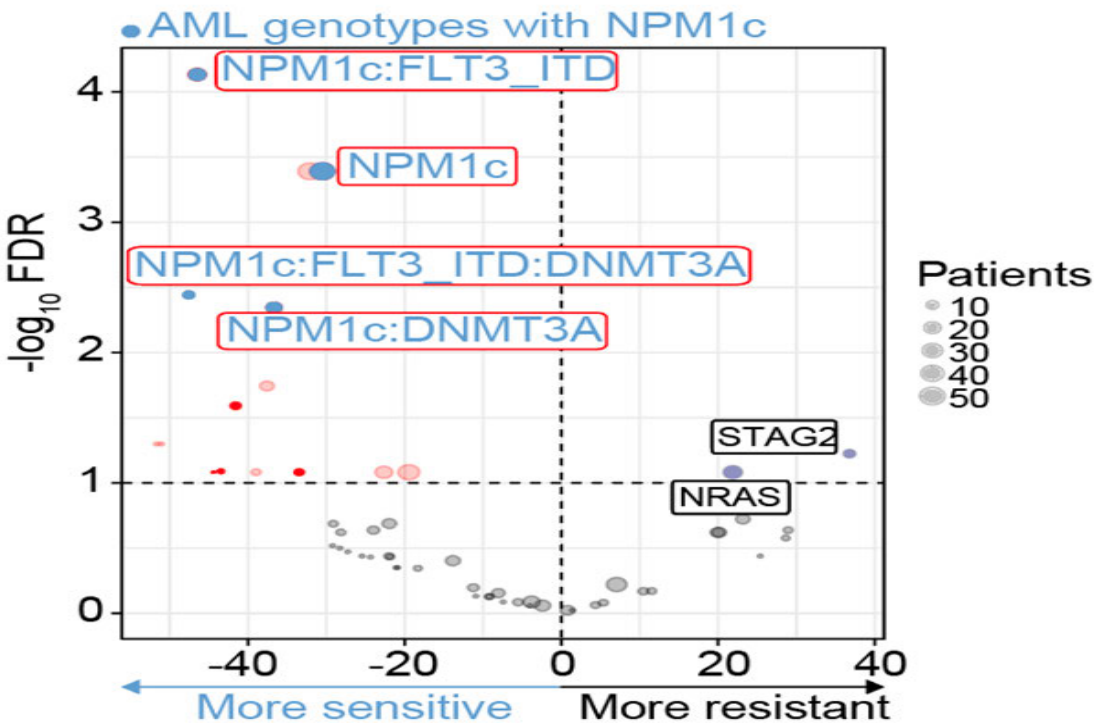
Multiple converging lines of evidence support the hypothesis that high *HOXA9* and *MEIS1* expression in AML creates a dependence on SYK signaling that can be exploited therapeutically. A comparison of AML proteomes with normal or high expression of *HOXA9* and *MEIS1* revealed that SYK protein was significantly more abundant in AML blasts with high *HOXA9/ MEIS1* expression (Mohr 2017). Moreover, there was an increase in SYK activation as a result of *MEIS1* driven Fc receptor and integrin-related signaling. This aberrant SYK signaling acts to drive the expression of genes necessary for cytokine independent growth and reinforces the *MEIS1* driven gene expression program through a positive feedback loop. The first-generation SYK inhibitor,

R788 (fostamatinib), was shown to have anti-leukemic activity and prolong survival in mouse models of *HOXA9/MEIS1* driven AML, including in patient-derived xenograft models. A publication from the Leukemia and Lymphoma Society's (LLS) Beat AML program explicitly established the link between *NPM1* mutation and dependency on SYK (Tyner 2018).

2.2 Preclinical and Clinical Rationale for the Investigation of Entospletinib in *NPM1*-mutated AML

Entospletinib (ENTO, formerly GS-9973) is a second generation, orally administered, selective ATP-competitive inhibitor of SYK. Kinase selectivity profiling has shown > 14-fold selectivity of ENTO for SYK vs other kinases compared with the less selective SYK inhibitor, fostamatinib (Braselmann 2006). In the aforementioned LLS study (Tyner 2018), bone marrow specimens from 572 newly diagnosed AML patients were genomically and transcriptomically profiled and tested ex vivo for sensitivity to 122 small molecule drugs including ENTO. Sensitivity to ENTO showed a statistically significant correlation with the presence of *NPM1* mutations (Figure 2).

Figure 2: Sensitivity of Primary Patient-derived AML Blasts to Ex Vivo Treatment With ENTO is Associated With *NPM1* Mutation



Abbreviations: AML, acute myeloid leukemia; ENTO, entospletinib; *NPM1*, *Nucleophosmin* 1

Note: X-axis is the fold change in sensitivity of the mutant vs the wild-type. The Y-axis shows the -$\log_{10}$ of the t-test False Discovery Rate-corrected p-value comparing drug response for the mutant vs wild-type subjects (Leukemia and Lymphoma Society Beat AML program, Brian Druker, personal communication).

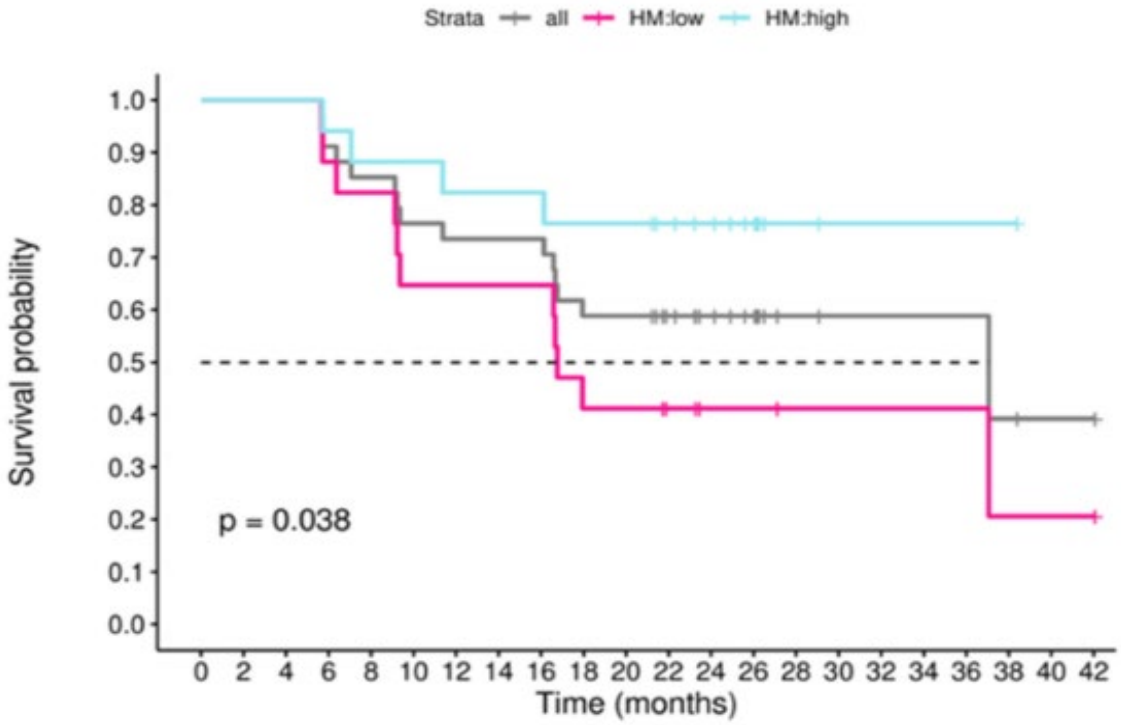
Phase 1b/2 Study of ENTO in AML (Study GS-US-339-1559)

Between July 2015 and September 2019, a Phase 1b/2 Study of ENTO in AML (GS-US-339-1559, NCT 02343939) enrolled 148 subjects in the US, Canada, and Germany into 3 treatment groups. One arm of this trial (Arm A) enrolled 53 previously untreated AML patients who were eligible for intensive induction. The median age for this cohort was 60 years and 30 subjects (57%) were in the ELN intermediate II or adverse prognostic category. Fourteen subjects, including 6 of 15 subjects with *NPM1* mutations had secondary AML. Subjects received a course of ENTO monotherapy for a 14-day lead-in period followed by the combination of ENTO with continuous infusion cytarabine for 7 consecutive days plus bolus daunorubicin for 3 consecutive days (7 + 3) induction and high-dose cytarabine consolidation. Doses of 200 mg twice daily (BID) and 400 mg BID were evaluated in the Phase 1b portion of the study (N = 12). ENTO was generally well-tolerated in combination with intensive induction chemotherapy. A maximally tolerated dose was not defined (there were no dose-limiting toxicities at either dose tested) and 400 mg BID was selected for study in the Phase 2 portion (N = 41) based on the limited incremental exposure at higher doses in earlier studies.

All 53 subjects across the Phase 1b and Phase 2 portions of the study were considered evaluable for efficacy. Thirty-seven subjects (70%) subjects achieved a CR or CR with incomplete recovery of neutrophil or platelet counts (CRi), including 13 of 15 *NPM1*-mutated subjects (87%). Among 10 subjects with rearrangement of the *MLL* gene (*MLL*-r), a mutation also associated with high baseline expression of *HOXA9* and *MEIS1*, 9 (90%) experienced a CR or CRi, including one patient who achieved a cytogenetic and morphologic CR after the ENTO monotherapy lead-in period. In contrast, the CR + CRi rate for the remaining 28 *MLL* and *NPM1* wild-type subjects was 54%. An exploratory retrospective analysis of *HOXA9* and *MEIS1* mRNA levels at baseline was performed for 34 subjects with available samples. Subjects with expression levels of *HOXA9/MEIS1* above the median for the overall group experienced superior overall survival compared to those with expression levels below the median (hazard ratio, 0.32; 95% confidence intervals, 0.100 to 0.997, p = 0.038) (Figure 3). Despite the small sample size and single-arm design of this study, higher CR/CRi rates in *NPM1*-mutated subjects and superior overall survival in the *HOXA9/MEIS1* high expressing subset are consistent with the hypothesis that SYK is a therapeutic dependency in this subset of AML and warrants further study.

The combination of ENTO with 7 + 3 induction and high dose cytarabine consolidation was generally well-tolerated with skin rash, liver transaminase elevations, and indirect hyperbilirubinemia being the most commonly reported ENTO-related toxicities (Section 2.4; Walker 2020).

Figure 3: Overall Survival in Newly Diagnosed AML Patients Treated With 7+3 and ENTO Induction.



Abbreviations: AML, acute myeloid leukemia; ENTO, entospletinib

Note: K-M curve in gray represents all 34 subjects. Light blue line represents subjects with *HOXA9/MEIS1* mRNA expression above the median level of expression (N = 17). The pink line is subjects with expression below the median (N = 17). OS is censored on the last date the subject was known to be alive (Walker 2020).

Phase 2 Study of ENTO in *NPM1*-mutant/*FLT-3* Wild -Type AML Patients (Study BAML-16-001-S6)

The activity of ENTO is currently being evaluated in the LLS Beat AML Master Trial, BAML-16-0001 (NCT03013998). This biomarker-based trial of newly diagnosed AML assigns subjects to treatment arms on the basis of their mutational profiles or other features.

Substudy 6, Cohort A (S6A) of this master protocol is evaluating the efficacy and safety of ENTO in subjects with *NPM1*-mutated/*FLT3* wild-type AML at a dose of 400 mg BID in combination with intensive induction therapy (7 + 3). Cohort 6A uses a Simon 2-stage design to reject the null hypothesis of a composite CR rate (CR + CR with partial hematologic recovery [CRh] + CR with incomplete hematologic recovery [CRi]) of 65% versus an alternative composite CR rate of 85%. To date, the safety profile of ENTO with 7 + 3 in this study has been generally consistent with that reported in the above-described GS-US-339-1559 study (Section 2.4).

2.3 Study Rationale

Given the role of SYK signaling in *HOXA9/MEIS1*-driven leukemic cell proliferation, the association between *NPM1* mutation and *HOXA9/MEIS1* dysregulation, and the preliminary promising results in early phase studies, the Sponsor will evaluate the efficacy and safety of ENTO in combination with intensive induction and consolidation chemotherapy in previously untreated AML patients with mutations in *NPM1*.

2.4 Benefit/Risk Assessment

NPM1-mutated AML constitutes a genetically defined subset of AML comprising approximately 30% of newly diagnosed subjects and is recognized as a distinct disease entity in the 2017 WHO classification of myeloid neoplasms and acute leukemia (Patel 2012, Arber 2016). *NPM1* mutation is commonly associated with normal cytogenetics in subjects < 60 years of age. In the absence of concurrent *FLT-3* internal tandem duplication (ITD) (or presence at low allelic ratio), or other adverse cytogenetic abnormalities, subjects with *NPM1* mutation are thought to be in the favorable risk category (Table 1) with CR rates of 86 to 88% with current standards of care (Angenendt 2019). Concurrent *FLT-3* ITD at high allelic ratio confers ELN intermediate risk status (Patel 2012, Dohner 2017). *NPM1*-mutated AML patients with additional adverse cytogenetic features are usually older than 60 years of age and/or have a history of myelodysplastic syndrome, and poorer prognosis with CR rates of 66.3% and a 5-year OS of 19.5% (Angenendt 2019).

As of 31 January 2021, 20 clinical studies of ENTO have been conducted in which approximately 1259 subjects received ENTO either alone or in combination with other agents. Detailed descriptions of ENTO clinical studies conducted to date including results, where available, may be found in the Investigator's Brochure (Section 4.0, Clinical Studies).

In the GS-US-339-1559 study, ENTO alone or in combination with 7 + 3 chemotherapy was generally well-tolerated. Most treatment-emergent adverse events (TEAEs) were consistent with those expected following treatment with intensive induction and consolidation chemotherapy as well as from complications of underlying AML. Commonly reported TEAEs/laboratory abnormalities are listed in Table 2.

Table 2: Common Treatment-emergent Adverse Events Reported in Study GS-US-339-1559 Regardless of Causality

TEAEs	Total n (%)	Grade 3 or 4 n (%)
Any TEAE	53 (100)	53 (100)
Nonhematologic AEs/laboratory abnormalities reported in > 25% of subjects		
Nausea	37 (70)	1 (2)
Diarrhoea	35 (66)	5 (9)
Oedema peripheral	31 (59)	0
Alanine aminotransferase increased	30 (57)	3 (6)
Blood bilirubin increased	26 (49)	6 (11)
Rash (maculopapular)	23 (43)	7 (13)
Decreased appetite	22 (42)	2 (4)
Constipation	21 (40)	0
Headache	21 (40)	0
Dyspnoea	20 (38)	2 (4)
Aspartate aminotransferase increased	19 (36)	2 (4)
Cough	18 (34)	0
Vomiting	18 (34)	0
Chronic kidney disease (decreased creatinine clearance)	17 (32)	1 (2)
Hypokalaemia	16 (30)	1 (2)
Insomnia	16 (30)	0
Fatigue	15 (28)	3 (6)
Abdominal pain	14 (26)	0
Creatinine increased	14 (26)	3 (6)
Dizziness	14 (26)	0
Hematologic AEs/laboratory abnormalities in > 25% of subjects		
WBC count decreased	49 (92)	49 (92)
Febrile neutropenia	44 (83)	44 (83)
Platelet count decreased	41 (77)	41 (77)
Lymphocyte count decreased	34 (64)	17 (32)
Anaemia	28 (53)	28 (53)
Neutrophil count decreased	19 (36)	19 (36)

Abbreviations: AE: adverse event; TEAE, treatment-emergent adverse events; WBC, white blood cell.

Source: Walker 2020

Grade ≥ 3 nonhematologic TEAEs reported in > 10% of study subjects included lung infection (n = 11, 21%), device-related infection (n = 9, 17%), hypoxia (n = 9, 17%), maculopapular rash (n = 7, 13%), hypertension (n = 6, 11%), and hyperbilirubinemia (n = 6, 11%).

Any grade rash was observed in 23 (43%) subjects (Table 2) including grade 3 rash in seven (13%) subjects. The rash was characterized as erythematous, diffuse, and morbilliform. Withholding ENTO improved the rash to Grade 1 within 10 days. Topical steroids and additional supportive care were used as deemed appropriate. The rash recurred in one of four subjects after rechallenge leading to discontinuation of ENTO. Hyperbilirubinemia was predominantly indirect, consistent with ENTO's known inhibitory effects on UDP-glucuronosyltransferase 1A1 (UGT1A1) leading to reversible increases in unconjugated bilirubin. Both rash and indirect hyperbilirubinemia were attributed to ENTO (Walker 2020).

Interim results from 26 patients treated with the combination of ENTO with 7 + 3 induction enrolled in the ongoing Study BAML-16-001-S6 (Cohort A) are also available through 01 October 2021. The median (range) duration of ENTO exposure for this cohort is 118 days (10, 613). The composite CR rate is 76% based on 25 patients evaluable for response. Safety data are generally consistent with those reported for Study GS-US-339-1559. Table 3 lists Grade ≥ 3 TEAEs reported in more than 1 subject. Two subjects experienced Grade 5 events, cerebrovascular accident and intracranial hemorrhage occurred in 1 subject each.

Table 3: Grade ≥3 TEAEs Reported in > 1 Subject from Study BAML-16-001-S6A

No. of treated patients, n (%)	**26 (100)**
Any Grade ≥ 3 TEAE	21 (81)
Nonhematologic TEAEs/laboratory abnormalities	
Device-related infection	3 (12)
Blood bilirubin increased	5 (19)
Sinusitis	2 (8)
Hyponatremia	3 (12)
Hypophosphatemia	4 (15)
Alanine aminotransferase increased	2 (8)
Alkaline phosphatase increased	2 (8)
Hypokalaemia	3 (12)
Sepsis	2 (8)
Hematologic TEAEs/laboratory abnormalities	
Febrile neutropenia	13 (50)
Anemia	9 (35)
Platelet count decreased	8 (31)
White blood cell count decreased	9 (35)
Neutrophil count decreased	6 (23)
Neutropenia	4 (15)
Thrombocytopenia	3 (12)
Lymphocyte count decreased	5 (19)
Leukopenia	2 (8)

Abbreviations: TEAE, treatment-emergent adverse events.

In summary, both the spectrum and frequency of TEAEs reported in association with the combination of ENTO and 7 + 3 induction and cytarabine consolidation were generally as expected for the underlying disease and treatment with intensive induction/consolidation chemotherapy. Rash, indirect hyperbilirubinemia, and transaminase elevations are specifically attributed to ENTO (Investigator's Brochure, Section 6.2.5). Toxicities observed to date with ENTO plus intensive induction/consolidation can be readily monitored and managed with close attention to standard safety assessments (eg, blood counts, electrolytes, liver function studies, fluid and electrolyte balance, and careful surveillance, treatment, and follow-up for infectious complications). The type and frequency of safety assessments described for the proposed study have been modeled to conform with those employed in Study GS-US-339-1559 and are in accordance with National Comprehensive Cancer Network (NCCN) supportive care recommendations. All are generally consistent with the standards of care for newly diagnosed AML patients undergoing intensive induction and consolidation chemotherapy.

Considering measures that are undertaken to minimize the risk to prospective study subjects, the potential risks identified in association with the combination of ENTO and intensive induction and consolidation chemotherapy are justified by the anticipated benefits that may be afforded to subjects with *NPM1*-mutated AML.

More detailed information about the known expected adverse drug reactions of ENTO may be found in the Investigator's Brochure (Section 6.1.2.2; Section 6.2).

2.4.1 COVID-19 Considerations

Patients undergoing systemic chemotherapy for cancer and leukemia have an increased risk of severe complications, some leading to death, following infection with coronavirus disease 2019 (COVID-19). This includes patients who have been fully vaccinated against the virus. The extent (if any) to which concurrent treatment with ENTO may increase the magnitude of risk is currently unknown. Prospective trial subjects including those who have been vaccinated against COVID-19, should be counseled to employ social distancing measures including the regular use of face coverings and avoidance of indoor congregant environments, especially those that include others for whom the vaccination and/or COVID-19 infection status are unknown.

Consult Appendix 9 for additional risk mitigation procedures potentially associated with clinical trial conduct in the COVID-19 pandemic era.

3.0 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of ENTO compared to placebo when added to chemotherapy in previously untreated *NPM1*-m AML, as defined by the rate of molecularly defined measurable residual disease (MRD).	• MRD negative CR rates after completion of 2 cycles of chemotherapy plus either ENTO or placebo. *Note:* MRD negative CR requires CR as defined by ELN 2017 criteria (with minor modification for neutrophil and platelet count thresholds as defined by the International Working Group [IWG]) as assessed by study site investigators, and MRD negativity (<0.01%) in bone marrow as measured by a molecular *NPM1*-m assay (eg, next generation sequencing) in a central laboratory upon recovery of peripheral blood counts following completion of 2 cycles of chemotherapy (ie, no later than Day 42 of Cycle 2).
Secondary	
• To evaluate the efficacy of ENTO compared to placebo when added to chemotherapy in previously untreated *NPM1*-m AML, as defined by relapse-free, event-free, and overall survival.	• Event-free survival, defined as the time from randomization to the earliest occurrence of induction treatment failure, relapse from CR, or death from any cause. *Note:* Induction treatment failure is failure to achieve morphological CR after completion of the last cycle of induction chemotherapy (no later than Day 42 of the last cycle of induction). • Relapse-free survival, defined as the time from CR until relapse or death from any cause as assessed by study site investigators. • Overall survival defined as the time from randomization until death from any cause.
• To evaluate the efficacy of ENTO compared to placebo when added to chemotherapy in previously untreated *NPM1*-m as defined by CR rate.	• CR rates after 2 cycles of chemotherapy, as defined by ELN 2017 criteria (with minor modification for neutrophil and platelet count thresholds as defined by the IWG) as assessed by study site investigators.
• To evaluate the safety of ENTO compared to placebo when added to intensive chemotherapy.	• Type, incidence, severity, and outcome of adverse events; changes from baseline in safety laboratory assessments, ECGs, ECHO/MUGA scans, ECOG PS.

Exploratory	
• To explore the predictive value of potential biomarkers that correlate with differential outcomes (CR, MRD negativity, event-free and overall survival) among ENTO- vs placebo-treated subjects.	• Baseline expression levels of *HOXA9/MEIS1* and other relevant genes in leukemic cells from peripheral blood and bone marrow aspirate using standard expression profiling platforms (eg, Nanostring® or next-generation sequencing) for correlations with response and progression. • Mutational profiling in leukemic cells using standard platforms like next generation sequencing for correlations with response and progression. • Targeted protein/phosphoprotein profiling (eg, pSYK expression) in leukemic cells at baseline for correlations with response and progression. • Extent of ENTO target engagement as measured by pSYK expression/expression of other relevant genes for correlation with response and progression. • Level of concordance for MRD for *NPM1*-m in leukemic cells derived from bone marrow aspirate and peripheral blood. • Log reduction in *NPM1*-m alleles in bone marrow post-induction compared with baseline for correlation with response and progression.
• To assess the value of MRD detection as a prognosticator of relapse.	• Longitudinal assessment of peripheral blood for detection of *NPM1*-m alleles among subjects who achieve MRD-negative CR post-Chemotherapy Cycle 2 using standard molecular platforms (eg, next-generation sequencing) for correlation with morphologic relapse.
• To further assess the PK of ENTO in combination with intensive induction therapy for population PK modeling. • To explore the relationship between CYP2C9 genetic polymorphisms and ENTO exposure. • To assess the relationship (if any) between cytidine deaminase polymorphisms and safety and efficacy outcomes.	• Population-based PK parameter assessment. • Identification of CYP2C9 polymorphisms and population-based PK analysis. • Correlation between cytidine deaminase polymorphisms and selected safety metrics and efficacy outcomes, described above.
• To compare changes in quality-of-life measures over time among subjects treated with ENTO compared to placebo when added to intensive induction therapy in previously untreated *NPM1-m* AML.	• EQ-5D-5L and EORTC-QLQ 30 over time.

Abbreviations: AML, acute myeloid leukemia; CR, complete response; ECG, electrocardiogram; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ELN, The European Leukemia Network; EORTC-QLQ 30, European Organization for Research and Treatment of Cancer Quality of Life

Questionnaire-Core 30; EQ-5D-5L, European Quality of Life 5 Dimensions Questionnaire; MRD, measurable residual disease; MUGA, multi-gated acquisition; *NPM1*-m, nucleophosmin-1 mutated; PK, pharmacokinetics; pSYK, phosphorylated spleen tyrosine kinase.

4.0 Study Design

4.1 Overall Design

This will be a multi-center, international, double-blind, placebo-controlled study in previously untreated subjects with AML harboring *NPM1* mutations. Upon fulfillment of all eligibility criteria, subjects will be randomized 1:1 to receive intensive chemotherapy in combination with either the SYK inhibitor, ENTO, or placebo. Randomization will be stratified by age (< 60 vs ≥ 60 years) and anthracycline administered during induction (daunorubicin vs idarubicin). The study will consist of Screening, Induction, Consolidation, End-of-Treatment, and Long-term Follow-up phases.

Subjects will undergo a screening bone marrow aspiration within 14 days prior to Cycle 1, Day 1 (C1D1) of induction for confirmation of diagnosis, morphology assessment (spicule prep), detection of cytogenetic abnormalities by cytogenetics/fluorescence in situ hybridization (FISH), and biomarker assessments (including *NPM1* and *FLT3* mutation status). In cases in which an adequate bone marrow aspirate cannot be obtained at Screening (eg, due to dry tap, hypocellularity or hemodilution), a trephine bone marrow biopsy is mandated.

NPM1 and *FLT3* mutational status will be assessed in a central laboratory designated by the sponsor. Mutation results obtained during a patient's routine diagnostic workup by the investigational site will be accepted for enrollment purposes as long as an appropriate sample is provided to the central testing facility selected by the Sponsor for companion diagnostic development AND the site can provide appropriate documentation pertaining to local assay performance characteristics and test validation prior to initiating enrollment in the study.

ENTO (400 mg) or placebo will be administered continuously BID beginning on C1D1 of induction chemotherapy (Table 4) through completion of consolidation (Table 5), including while awaiting blood count recovery.

Table 4: Induction Chemotherapy

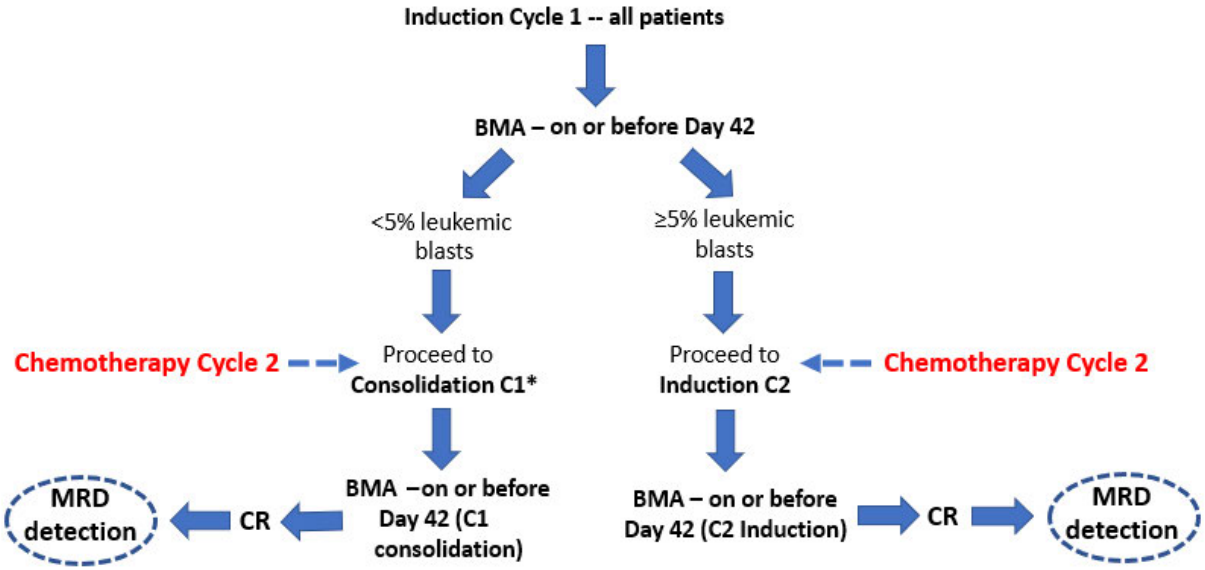
	Age < 60 years	**Age ≥ 60 years**
Cycle 1:		
Cytarabine[a]	100 mg/m^2 by continuous infusion, Days 1-7	100 mg/m^2 by continuous infusion, Days 1-7
Anthracycline	Daunorubicin, 60 mg/m^2 slow IV push, Days 1-3 ***OR*** Idarubicin, 12 mg/m^2 slow IV push, Days 1-3	Daunorubicin, 60 mg/m^2 slow IV push, Days 1-3 ***OR*** Idarubicin, 12 mg/m^2 slow IV push, Days 1-3
Cycle 2 (if administered):		
Cytarabine	1.0 g/m^2, BID Days 1-6	1.0 g/m^2, BID Days 1-6
Anthracycline	Daunorubicin, 60 mg/m^2 slow IV push, Days 1-3 ***OR*** Idarubicin, 12 mg/m^2 slow IV push, Days 1-3	N/A

Abbreviations: BID, twice daily; IV, intravenous; N/A, not administered.

[a] Subjects who are candidates for continuous infusion of cytarabine in Cycle 1 at doses higher than 100 mg/m^2/day are ineligible.

Subjects will undergo bone marrow examination no later than Day 42 of Induction Cycle 1 for assessment of response. Subjects with ≥5% residual leukemic blasts in bone marrow will receive Induction Cycle 2 as outlined in Table 4, which may be administered prior to blood count recovery. Subjects with <5% residual blasts will receive Consolidation Cycle 1 as outlined in Table 5 upon recovery of peripheral blood counts (absolute neutrophil count [ANC] > 1.0 x 10^9/L; platelet count > 100 x 10^9/L). After completion of Induction Cycle 2 or Consolidation Cycle 1 (hereafter referred to collectively as Chemotherapy Cycle 2), subjects will undergo bone marrow examination for assessment of remission status at the investigative site (bone marrow biopsy is mandated if sufficient or adequate aspirate cannot be obtained, eg, due to dry tap, hemodilution or hypocellularity). Bone marrow examination should await recovery of ANC to > 1.0 x 10^9/L and platelet count to > 100 x 10^9/L no later than Day 42 of Chemotherapy Cycle 2, unless leukemic progression is suspected. Subjects who achieve or remain in morphologic CR after Chemotherapy Cycle 2 will undergo MRD assessment in peripheral blood and bone marrow aspirate in a central laboratory designated by the Sponsor. Subjects who have not achieved morphologic CR after the last cycle of induction (whether it be Induction Cycle 1 or Induction Cycle 2) will be deemed treatment failures. Figure 4 provides a schematic representation of the study treatment plan from Cycle 1, Day 1 through completion of Chemotherapy Cycle 2.

Figure 4 Treatment Phase: Cycle 1, Day 1 through Completion of Chemotherapy Cycle 2:



* Following recovery of ANC to >1.0 x 10^9 /L and platelet count to >100 x 10^9/L
BMA, bone marrow aspirate; MRD, measurable residual disease

Subjects who achieve MRD negative CR post-Chemotherapy Cycle 2 will undergo retrospective MRD assessments in peripheral blood every 3 months until morphologic relapse.

All subjects who achieve morphologic CR, CRh, or CRi upon completion of Chemotherapy Cycle 2 may initiate or continue consolidation therapy in combination with ENTO or placebo (in accordance with their original randomized treatment assignment), as outlined in Table 5 at the investigator's discretion either instead of or as a bridge to hematopoietic stem cell transplant.

Table 5: Treatment Phase –Consolidation

	Age < 60 years	Age ≥ 60 years
Cytarabine	3.0 g/m^2, BID over 3 hours on Days 1, 3 and 5 every 28-35 days for up to 3 cycles*	1.5 g/m^2, BID over 3 hours on Days 1, 3 and 5 every 28-35 days for up to 3 cycles*

For subjects with < 5% residual blasts post-Induction Cycle 1, Consolidation Cycle 1 will consist of Chemotherapy Cycle 2. For patients with ≥5% residual blasts post-Induction Cycle 1, Induction Cycle 2 (Table 4) will consist of Chemotherapy Cycle 2 with consolidation beginning thereafter. All subjects are eligible to receive up to 3 cycles of high dose cytarabine after Chemotherapy Cycle 2.

All subjects will undergo an End-of-Study Treatment Visit 30 ± 7 days after the last study treatment (either ENTO/placebo or chemotherapy, whichever is later) or prior to initiation of follow-on therapy (eg, maintenance therapy, HSCT), if sooner than 30 ± 7 days after last study treatment.

All subjects regardless of their post-remission status will be followed monthly for 3 months after the End-of-Study Treatment Visit and thereafter at least once every 3 months for progression/relapse, first salvage therapy, and survival until study termination. Unscheduled study visits at other time points are permitted in the setting of suspected leukemic recurrence or for evaluation and management of post-treatment sequelae.

4.2 Justification for Dose of ENTO

The dose of ENTO that will be investigated in this study is 400 mg orally (PO) every 12 hours, consistent with that employed in aforementioned early phase studies in AML (see Section 2.2).

Pharmacokinetic (PK) data derived from healthy volunteers demonstrated significantly less than dose-proportional increases in exposure when comparing 800 mg and 400 mg BID dosing schedules, suggesting a plateau in exposures that is likely due to solubility-limited absorption of ENTO. The median maximal concentration (C_{max}) and area under the concentration time curve at steady state (AUC_{ss}) were approximately 30% and 23% higher when comparing 800 mg BID with 400 mg BID doses, respectively, in healthy subjects.

Preliminary safety exposure-response analyses, which included a total of 191 subjects from Studies GS-US-339-0102 in subjects with relapsed or refractory hematologic malignancies (Section 4.2.1 of the IB) and GS-US-339-1559, who received ENTO monotherapy or in combination with 7 + 3 chemotherapy, showed that the exposure distributions were similar in subjects who experienced any grade adverse events (AEs), except for a higher median AUC_{ss} observed in subjects with any grade alanine aminotransferase increase or hyperbilirubinemia. Since ENTO is an inhibitor of the UGT1A1 enzyme, the Sponsor investigated the exposure-response relationship between the maximal change from baseline in total bilirubin, and the maximal and minimal change from baseline in direct bilirubin. While there was no clear exposure-response relationship for the minimal or maximal change from baseline in direct bilirubin, exploratory modeling suggests that a linear exposure-response relationship exists between ENTO AUC and the maximal change from

baseline in total bilirubin, consistent with the effects of UGT1A1 inhibition on the levels of indirect (unconjugated) bilirubin. These observations are consistent with an earlier analysis in chronic lymphocytic leukemia subjects, where no clinically relevant trends were observed between ENTO exposure and safety (either clinical adverse events or laboratory abnormalities), except for a trend towards higher total bilirubin levels with higher ENTO exposures (Gupta 2017).

In the Phase 1 study GS-US-245-0101 in healthy volunteers and subjects with rheumatoid arthritis (Section 4.1.1. of the IB), increasing pharmacodynamic modulation of CD63 and pSYK (Y525) was observed with increasing dose and ENTO exposures until reaching a plateau in exposure in healthy volunteers.

4.3 End of Study Definition

The study will be completed when all enrolled subjects either relapse, die, or after the last subject enrolled completes 5 years of follow-up, whichever is earliest.

5.0 Study Population

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Adults 18 to 74 years with previously untreated *de novo* AML, AML with MDS features, or therapy-related AML, who are candidates for intensive induction therapy.
2. *NPM1*-mutated disease documented in a local or the Sponsor's central testing facility.

   Note: Subjects with local test results for *NPM1*-m (and/or *FLT3* mutational status) may enroll, provided appropriate samples are sent to the Sponsor's central testing facility for *NPM1*-m companion diagnostic development (see Section 4.1).
3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0, 1, or 2.
4. Adequate hepatic and renal function defined as:
   a. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 times the upper limit of normal (ULN), except those with hepatic involvement by AML, as documented by either computed tomography (CT) or ultrasound, in whom levels of AST and ALT < 5 times ULN are acceptable; total bilirubin < 1.5 times ULN unless elevated due to Gilbert's Disease or hemolysis.
   b. Calculated creatinine clearance > 40 mL/min or serum creatinine < 1.5 times ULN.
5. Prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR) ≤ 1.5 x ULN unless receiving therapeutic anticoagulation. *Note*: Transition from a Vitamin K or Factor Xa antagonist to a low-molecular weight heparin preparation is recommended prior to the start of induction chemotherapy (see Appendix 8 for guidelines on anticoagulation management).
6. Left ventricular ejection fraction ≥ 45% confirmed by echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan.
7. Negative serum ß-HCG test in women of childbearing potential (WOCBP).
8. For WOCBP, willingness to abstain from heterosexual intercourse OR to use a protocol-recommended method of contraception from 7 days prior to C1D1 throughout the study treatment period and for 90 days following the last dose of ENTO/placebo or as recommended in the prescribing information for other co-administered study drugs (whichever is later). See Appendix 3 for contraceptive guidance.
9. For male subjects with female sexual partners of childbearing potential, willingness to abstain from heterosexual intercourse OR use a protocol recommended method of contraception beginning 7 days prior to C1D1 throughout the study treatment period and for 90 days following the last dose of ENTO/placebo or as recommended in the prescribing information for other co-administered study drugs (whichever is later), AND to refrain from sperm donation from the start of study treatment throughout the study

treatment period and for 90 days following the last dose of ENTO/placebo or as recommended in the prescribing information for other co-administered study drugs (whichever is later). See Appendix 3 for contraceptive guidance.

10. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
11. Willingness to comply with scheduled study visits, procedures, and treatment plan.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Isolated myeloid sarcoma (ie, participants must have peripheral blood and/or bone marrow involvement by AML) or acute promyelocytic leukemia.
2. Concurrent *FLT3* mutation (either TKD or ITD).
3. Known central nervous system (CNS) involvement with leukemia.
4. Is a candidate for more intensive treatment than specified in this protocol.
5. Either not a candidate for any anthracycline therapy or a candidate for induction therapy with a higher dose of daunorubicin (eg. 90 mg/m^2).
6. Is a candidate for daily doses of cytarabine > 100 mg/m^2 in Induction Cycle 1.
7. Active infection with hepatitis B, C, or uncontrolled human immunodeficiency virus (HIV).

   Note: Subjects who are positive for hepatitis B surface antigen (HBsAg) are ineligible. Those who are seropositive for hepatitis B core antibody (anti-HBc) may enroll but must agree to receive hepatitis B virus (HBV) prophylaxis during the study treatment period and undergo regular surveillance for HBV reactivation at least once every 3 months. Subjects who have received curative therapy for prior HCV infection and who are seropositive for hepatitis C antibody (anti-HCV), may enroll, however must undergo regular surveillance monitoring for HCV reactivation.

   Note: At the discretion of the investigator and in accordance with institutional as well as local health authority guidelines and regulations regarding participation of HIV + patients in clinical trials, HIV + patients may enroll in this study if all of the following parameters are fulfilled:

   - CD4+ lymphocyte count >350 cells/µL
   - Patient is receiving highly active antiretroviral therapy (HAART) for a period of at least 4 weeks prior to initiation of study treatment AND has an HIV viral load of <400 viral copies/mL.

- Commitment by the patient to continue HAART for the duration of study treatment.

Please note that components of some anti-retroviral therapy combinations may pose a risk for drug interactions with ENTO. For example, combinations that include ritonavir may not be concurrently administered with ENTO because ritonavir is a moderate inducer of CYP2C9. Since CYP3A is a minor pathway for ENTO metabolism, concurrent use of HAART combinations that include cobicistat are allowed. Before considering an HIV + patient who meets the above entry criteria for enrollment, investigators are encouraged to consult with either the Sponsor or a pharmacist at their institution in order to ensure that potential trial subjects are not subjected to the risk of unwanted interactions between the study medication and the patient's anti-retroviral therapy.

8. Known active coronavirus disease 2019 (COVID-19) either symptomatic or asymptomatic, as determined by nasopharyngeal swab for severe acute respiratory syndrome (SARS) coronavirus 2 (SARS CoV-2) RNA or antigen.

   Note: Subjects with a history of SARS-CoV-2 nasopharyngeal carriage (either with or without symptoms), who have subsequently tested negative on follow-up nasopharyngeal swab and are without signs or symptoms of COVID-19 may enroll. Subjects who are fully vaccinated against SARS-CoV-2 may enroll.

9. Disseminated intravascular coagulation with active bleeding or signs of thrombosis.

10. History of prior allogeneic hematopoietic stem cell transplant or solid organ transplant.

11. History of non-myeloid malignancy except for the following: adequately treated localized basal cell or squamous cell carcinoma of the skin; cervical carcinoma in situ; superficial bladder cancer; asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy (which may be continued while on study) and with normal prostate specific antigen for > 1 year prior to start of study therapy; or any other cancer that has been in complete remission without treatment for ≥ 3 years prior to enrollment.

    Note: Subjects who are on adjuvant hormonal therapy and ≥ 3 years from definitive therapy for their primary tumor are eligible to enroll.

12. Current (within 30 days of study enrollment) drug-induced liver injury, chronic active hepatitis, alcoholic liver disease, nonalcoholic steatohepatitis, primary biliary cholangitis with inadequate response to ursodeoxycholic acid or other health-authority approved therapy, extrahepatic obstruction caused by cholelithiasis, cirrhosis of the liver, or portal hypertension.

13. Ongoing (within 6 weeks of study enrollment) hepatic encephalopathy.

14. Treatment with proton pump inhibitors (PPIs) from 7 days prior to enrollment until 48 hours after completion of ENTO or placebo.

    Note: PPIs are likely to interfere with ENTO absorption, thus requiring a 7-day washout period prior to the initiation of study medication. For management of acute gastrointestinal bleeding during the study treatment period (such as that related to

chemotherapy), short term concurrent use of PPIs is permitted for up to 10 consecutive days. If longer durations of PPI exposure are required, subjects should discontinue study medication. H_2 receptor antagonists and antacids are allowed throughout the study treatment period.

15. Ongoing immunosuppressive therapy, including systemic chemotherapy for treatment of leukemia.

    Note: Subjects may not receive AML-directed therapy prior to enrollment other than hydroxyurea or leukapheresis for acute management of hyperleukocytosis.

16. Concurrent (within 14 days of study enrollment) participation in an investigational drug study with therapeutic intent.
17. Clinical signs/symptoms of leukostasis that have failed therapy including hydroxyurea and/or leukapheresis of at least 3 days duration.
18. Clinically significant heart disease defined as:
    a. New York Heart Association Class 3 or 4 congestive heart failure,
    b. Acute myocardial infarction ≤ 6 months before enrollment,
    c. Symptomatic cardiac ischemia/unstable angina ≤ 3 months before enrollment,
    d. History of clinically significant arrhythmias (eg, ventricular tachycardia or fibrillation; Torsades de Pointe) including Mobitz type II 2nd degree or 3rd degree heart block without a permanent pacemaker in place.
19. Subjects with a corrected QT interval (using the Fredericia formula, QTcF) > 480 msec or Long QT Syndrome
20. Evidence of ongoing, uncontrolled systemic bacterial, fungal, or viral infection at the time of study treatment initiation, including but not limited to persistent fever or positive cultures in the setting of appropriate antimicrobial therapy. Patients who are afebrile for ≥48 hours may enroll even while continuing antimicrobial therapy.
21. Pregnant or breastfeeding women.
22. Alcohol or drug addiction as determined by investigator.
23. Unable to swallow tablets or concurrent disease affecting gastrointestinal function such as, malabsorption syndrome, gastric or small bowel resection, bariatric surgery, inflammatory bowel disease, or bowel obstruction.
24. Any prior or ongoing condition that, in the opinion of the investigator, could adversely affect the safety of the subject or impair the assessment of study results.
25. Known hypersensitivity to ENTO, cytarabine, daunorubicin, or idarubicin, their metabolites, or formulation excipient.

5.3 Lifestyle Considerations

No lifestyle changes or restrictions are required for clinical trial participation.

6.0 Study Treatment and Concomitant Therapy

6.1 Study Treatment Administered

Study medication (ENTO, 400 mg or placebo) will be administered orally approximately every 12 hours and should be taken at approximately the same time each day while in the fasted state (≥ 2 hours after and at least 1 hour before a meal) with 8 ounces of water. Tablets should be swallowed whole. Subjects who have a delay of < 6 hours in administration of a dose of study medication should take the planned dose as soon as possible after the intended time of administration. For subjects who have a delay of ≥ 6 hours, the missed dose should not be taken and the time frame for the subsequent dose of study medication should be maintained. Vomited doses should not be repeated *except* if the tablets are clearly visible in the vomitus.

For cytarabine and daunorubicin or idarubicin, follow the currently approved prescribing information and institutional guidelines when administering.

6.2 Preparation/Handling/Storage/Accountability

ENTO is available as 200 mg film-coated tablets (entospletinib bis-methanesulfonate monohydrate spray-dried dispersion formulation or ENTO SDD). ENTO tablets or placebo-to-match tablets are packaged in a white, high-density polyethylene bottle with silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous-thread, child-resistant, polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner. The study medication should not be transferred into a container other than that in which it was supplied in order to ensure its stability. Study medication should be stored at 15°C to 30°C (59°F to 86°F).

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study medication and any discrepancies are reported and resolved before use. Only participants enrolled in the study may receive study medication and only authorized site staff may supply or administer it.

All study medication must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. Measures that minimize medication contact with the body should always be considered during handling, preparation, and disposal procedures. Any unused study medication should be disposed of per the local requirements. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study medication accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study medication are provided in the Study Reference Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

All subjects who sign informed consent will be registered through an Interactive Voice/Web Response System (IxRS). Subjects who subsequently meet all eligibility requirements will be randomly assigned 1:1 to study medication (ENTO or placebo) using the IxRS. The randomization

will be stratified by age (< 60 vs ≥ 60 years) and anthracycline administered during induction (daunorubicin or idarubicin). All subjects, study site personnel, and the Sponsor's clinical trial management staff (and their designees) will be blinded to treatment assignment.

Members of the Data Monitoring Committee (DMC; Section 9.5) may be unblinded to treatment assignment for individual subjects or treatment arm in order to better assess safety and efficacy trends that could potentially underlie the basis for specific recommendations to modify the study. The criteria and procedures for unblinding at the DMC are outlined in the DMC Charter. Investigators will also have the ability to unblind the study medication assignment for individual patients in cases of medical emergency or where this information is critical for the assessment and management of specific adverse events (eg. suspected, unexpected, serious adverse reactions [SUSARs]) including Grade 5 AEs assessed as at least possibly related to study medication. The investigator will have the capability to unblind the study medication assignment without prior authorization from the study medical monitor or Sponsor and will access study medication assignment via the IxRS. Upon unblinding the medication assignment for a specific patient, the investigator must notify the study's medical monitor as soon as possible.

6.4 Compliance with Study Medication Regimen

Compliance with the study medication dosing schedule will be documented at each study visit via diary cards placed in the subject's medical record and entered in the electronic case report form (eCRF) at each scheduled visit. Deviation(s) from the prescribed dosing schedule will be recorded.

6.5 Dose Modification

Toxicity management and dose modifications for chemotherapy should follow institutional standards of care in accordance with health authority guidelines as outline in the relevant prescribing information for each country.

6.5.1 ENTO/Placebo

Hematologic toxicity: There will be no dose modifications for hematologic toxicity except in subjects who achieve a CR with count recovery followed by recurrence of cytopenias that are not attributable to subsequent chemotherapy or other causes. In this setting, performance of a bone marrow aspirate and/or biopsy to confirm AML has not recurred is mandated. Interrupt study medication for Grade 4 neutropenia or thrombocytopenia attributed to study medication until counts return to Grade 2 or better. Study medication may then be restarted at a 50% reduced dose twice daily. If Grade 4 neutropenia or thrombocytopenia recurs, the total daily dose may be further reduced to 50% once daily. No further dose level reductions beyond this are permitted and subjects should be removed from study medication if Grade 4 neutropenia or thrombocytopenia recurs. If blood counts remain stable for 1 month after dose reduction, investigators may attempt to increase the dose of study medication by one dose level.

Dose modifications for non-hematologic toxicities are described in Table 6.

Table 6: Study Treatment Modifications for Non-hematologic Toxicities

Liver function abnormalities:	• For Grade 1-2 abnormalities, continue study medication at full dose. • For Grade ≥ 3 AST/ALT elevations, interrupt study medication and recheck transaminase levels at least weekly. • When AST, ALT levels return to Grade 1 or baseline, restart study medication at a 50% reduced dose twice daily. • If there is no recurrence of Grade ≥ 3 transaminase elevation after 2 weeks of reduced dose, escalation to full dose may be attempted. • For Grade ≥ 3 increased blood bilirubin not attributed to increased indirect bilirubin levels, or liver function abnormalities that meet the criteria for Hy's law**, permanently discontinue therapy. *Note:* ENTO is an inhibitor of UGT1A1 and reversible increases in unconjugated (indirect) bilirubin values have occurred in healthy subjects receiving ENTO. In the absence of symptoms or other liver function abnormalities, study medication dose modification is not required for elevated indirect bilirubin levels.
Dermatologic abnormalities:	• For all Grade 1 to 2 abnormalities that are clinically manageable with topical steroids, continue study medication. • For Grade 3 rash, interrupt study medication until rash resolves to Grade 1. At this time, restart at a 50% reduced dose twice daily. • If Grade 3 rash does not recur after 2 weeks of reduced dose study medication, escalation to full dose may be attempted. • Permanently discontinue study medication in subjects with Grade 4 rash or those with recurrent Grade 3 rash despite dose reduction.
Gastrointestinal toxicity:	• For Grade 3 diarrhea attributed to study medication, anti-diarrheal medication should be initiated in an effort to achieve improvement. If this does not control diarrhea then study medication should be interrupted until diarrhea resolves to Grade 1 or less. Study medication may then be restarted at a 50% reduced dose twice daily. • If Grade 3 diarrhea does not recur after 2 weeks of reduced dose study medication, escalation to full dose may be attempted.

	• For Grade 4 diarrhea, permanently discontinue study medication.
Pneumonitis:	*Note:* Non-infectious pneumonitis is a diagnosis of exclusion and a thorough evaluation for infectious etiologies is mandated. • If Grade 1 non-infectious pneumonitis develops, it is acceptable to observe closely while continuing study medication. • If Grade 2 pneumonitis develops, interrupt study medication until Grade 1 or less. A short course of prednisone or methylprednisolone may be given for Grade 2 pneumonitis. • Following resolution to Grade 1, restart study medication at a 50% reduced dose twice daily. This dose level should be maintained without attempt to escalate to full dose. • If Grade 3 or 4 pneumonitis develops, study medication should be discontinued permanently.
Other non-hematologic toxicities:*	• Subjects who experience other Grade ≥3 nonhematologic toxicity assessed as at least possibly related to study medication, interrupt until the toxicity resolves to Grade 1, and then restart at 50% reduced dose twice daily and continue through the end of the cycle. • If toxicity recurs at this lower dose, study medication will be discontinued permanently.

* Excluded from this requirement are electrolyte disturbances, nausea, vomiting, or diarrhea that are reversible with supportive care within 48 hours. Since subjects will be receiving the study medication daily, low grade chronic side effects, such as nausea, fatigue, and diarrhea, while not meeting the above criteria for dose modification, may not be tolerable when experienced for long periods of time. Following discussion with the medical monitor, dose reduction may be permitted if low grade chronic side effects cannot be managed effectively with supportive care, as long as they are attributed to study medication.

** A Hy's law case is one in which liver aminotransferase levels ≥3x ULN are accompanied by an elevation of total bilirubin to >2x ULN without initial findings of cholestasis (e.g. elevated serum alkaline phosphatase levels), for which no other reason can be found to explain the combination of increased transaminase levels and total bilirubin, such as viral hepatitis A, B or C; pre-existing or acute liver disease; or another drug capable of causing the observed liver injury.

If the following signs or symptoms are medically manageable, they are not to be a consideration with respect to the subject's study medication dose or continuation of study treatment: nausea, mild vomiting, diarrhea, drug-related fever or chills, transient and correctable laboratory test abnormalities, line associated thrombosis, or alopecia. Subjects who are intolerant of study medication beyond Induction Cycle 1, may either permanently discontinue it or interrupt study medication in consultation with the medical monitor until the toxicity or laboratory abnormality has resolved to Grade 1 or baseline following which, dose reduction may be considered.

6.5.2 Cytarabine Consolidation Therapy Dose Modifications

In the setting of neurotoxicity attributed to cytarabine, contributions of concomitant medications should be assessed, and other medications discontinued if possible. For neurotoxicity Grade ≥ 2 due to cytarabine therapy, discontinue cytarabine for the remainder of the cycle. Resumption of cytarabine may be considered at the next chemotherapy cycle at a reduced dose per institutional standards of care if the toxicity has resolved. For a second occurrence of neurotoxicity Grade ≥ 2, cytarabine should be permanently discontinued.

6.5.3 Retreatment Criteria

Resumption of study medication at a later date is not permitted in subjects who permanently discontinue.

6.6 Continued Access to Study Medication After the End of the Study

Study medication will be discontinued for all subjects no later than at the completion of consolidation.

6.7 Treatment of Overdose

Any dose of study medication greater than the dose assigned is considered an overdose. Adverse events associated with an overdose will be recorded on the AE eCRF log. Events that meet the criteria for seriousness must be reported immediately, without undue delay, after awareness via the serious adverse event (SAE) reporting process (see Appendix 2). In the event of an overdose, contact the medical monitor immediately. The subject must be monitored for evidence of toxicity and standard supportive treatment should be provided, as necessary. It is unknown whether ENTO can be removed by dialysis. There is no known antidote for ENTO. In the case of symptomatic overdose, the subject should receive standard treatment for overdose and supportive therapy based on the subject's signs and symptoms.

6.8 Concomitant Therapy

All concomitant medications will be recorded beginning on C1D1 through 30 ± 7 days after treatment completion. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapies.

Subjects should receive full supportive care including transfusions of blood and blood products, antibiotics, antiemetic and antifungal medications, allopurinol, etc., as appropriate. Patients should receive prophylactic antimicrobial therapy in accordance with institutional standards of care. No other direct antileukemic therapy is permitted except for hydroxyurea prior to Induction Cycle 1 to control hyperleukocytosis, as required. The use of myeloid growth factors is permitted according to guidelines for use in AML but is generally discouraged during induction. For consolidation therapy, GM-CSF or G-CSF may be used in accordance with National Comprehensive Cancer Network guidelines (NCCN Guidelines) or per institutional standards of care.

Adrenocortical replacement therapy, ie, ≤ 10 mg/day prednisone or equivalent, is allowed. Short term administration of dexamethasone for prophylaxis against chemotherapy-induced nausea and

vomiting or toxicities associated with high dose cytarabine is also permitted as is administration of "stress" doses of steroids for management of sepsis with or without hypotension. Non-systemic (eg, topical, intraocular) steroids are permitted, as needed.

Recombinant erythropoietin is not permitted at any time during the study. Palliative radiation therapy may not be administered while the subject is on study except for the management of localized skin lesions.

Subjects should NOT receive a PPI during therapy with study medication except if required for management of acute gastrointestinal bleeding and only for a period of up to 10 consecutive days (Section 5.2). If longer durations of PPI exposure are required, subjects should discontinue study medication. H_2 receptor antagonists and agents such as locally acting antacids (eg, TUMS) and carafate are allowed to control symptoms of gastritis.

ENTO is a substrate of CYP2C9 and CYP3A. Co-administration of rifampin (a strong CYP3A and moderate CYP2C9 inducer) resulted in an approximately 70% decrease in ENTO exposure (Section 6.1.2.1, Investigator's Brochure). As such, co-administration of strong CYP3A and CYP2C9 inducers, and moderate CYP2C9 inducers must be avoided beginning 14 days prior to study drug administration and throughout the study treatment period (Appendix 7). Co-administration with fluconazole, a CYP2C9 inhibitor, increased ENTO exposure by approximately 40%. Caution should be exercised when co-administering drugs that are moderate to strong inhibitors of CYP2C9. Neither itraconazole nor posaconazole are inhibitors of CYP2C9 and can be safely co-administered orally with study medication, if clinically indicated.

ENTO is expected to produce asymptomatic and transient elevations of unconjugated (indirect) bilirubin due to inhibition of UGT1A1. The elevations in indirect bilirubin in previous studies were generally self-limited and did not result in discontinuation of ENTO (Section 6.1.2.2, Investigator's Brochure).

ENTO marginally increased the exposure of the P-glycoprotein substrate, digoxin, thus caution should be exercised when co-administering medications that are transported by P-glycoprotein.

ENTO increased the exposure of the OATP1B1, OATP1B3, and BCRP substrate, rosuvastatin, by approximately 3.8-fold, which may theoretically increase the risk of rhabdomyolysis. In reviewing the safety of subjects who have received an HMG-CoA reductase inhibitor concurrently with ENTO, there have been no reports of rhabdomyolysis nor a difference in adverse events profile. As a precautionary measure, reduce doses of HMG-CoA reductase inhibitors administered concurrently with study medication as outlined in Appendix 7. In general, caution should be exercised when co-administering medications that are transported by OATP1B1, OATP1B3, or BCRP; dose adjustment may be necessary, if clinically indicated (Section 6.1.2.1, Investigator's Brochure).

For HIV + patients who meet all criteria for enrollment outlined in Section 5.2, sites are encouraged to consult with the Sponsor or their institutional pharmacist in order to assess the potential for adverse interactions between the study medication and one or more components of their anti-retroviral therapy combination, before enrolling the patient.

7.0 Discontinuation of Study Treatment/Participation

7.1 Discontinuation of Study Treatment

Subjects may discontinue study medication at any time at his/her own request or may be discontinued at the discretion of the investigator for safety, behavioral, or compliance reasons.

Subjects must discontinue study medication for the following reasons:

- Recurrence of leukemia after a response
- Failure to achieve (or maintain) CR, CRh or CRi post-Chemotherapy Cycle 2
- Death
- Withdrawal of consent
- An AE or intercurrent illness that precludes further administration of protocol therapy or participation in the study
- Need for, or use of a prohibited concomitant medication
- Hematopoietic stem cell transplantation
- Pregnancy

If study treatment is permanently discontinued for any reasons, subjects shall remain in the study for long-term follow-up. See Table 7 for assessments required for the End-of-Treatment evaluation and long-term follow-up.

7.2 Discontinuation from the Study

Subjects may withdraw from the study at any time at his/her own request or may be withdrawn at the discretion of the investigator for safety, behavioral, or compliance reasons. Subjects must discontinue study participation for the following reasons:

- Death
- The study is terminated by the Sponsor

7.3 Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 Study Assessments and Procedures

The schedule of study assessments and procedures is summarized in Table 7.

All study visits should be scheduled relative to the C1D1 date regardless of any treatment interruptions. Acceptable windows for study visits/assessments after C1D1 are ± 1 day. Unscheduled study visits may be required as clinically indicated for evaluation of AEs or suspected leukemic relapse/progression. Results of diagnostic evaluations performed as part of an unscheduled study visit must be entered into the Unscheduled Visit eCRF.

Table 7: Schedule of Assessments and Procedures

Study Phase	**Screening**	**Induction (up to 2 Cycles)***					**At Recovery of Blood Counts/Assessment of Remission Status (Post-Induction Cycle 1, Post-Chemotherapy Cycle 2)/ At Relapse**	**Consolidation (up to 3 Cycles)***				**End-of-Study Treatment**	**Long-Term Follow-up** [x]
Study Visit Day [a]	-14 to 0	1	3	7	14	15 until blood count recovery		1	3	5	28 to 35	30 ± 7 days after last study treatment	
Informed consent	X												
IxRS registration/ randomization	X												
Medical/smoking history/ prior medications/AML baseline characteristics [b]	X												
Safety assessments													
Vital signs [c]	X	X	X	X	X			X	X	X	X	X	
Physical examination [d]	X	X			X		X	X			X	X	
Height/weight [e]	X				X			X				X	
ECG [f]	X												
ECHO/MUGA [g]	X											X	
ECOG PS (Appendix 6)	X	X			X						X	X	
AEs/concomitant medications [h]	X	X	X	X	X			X	X	X	X	X	
Hematology [i]	X	X	X	X	X	X	X	X			X	X	
Clinical chemistries/ LFTs [j]	X	X	X	X	X		X	X			X	X	
Coagulation [k]	X	X	X	X	X								
Urinalysis [l]	X												
ß-HCG/FSH [m]	X	X						X				X	
HBV/HCV/HIV serologies [n]	X												

Study Phase	**Screening**	**Induction (up to 2 Cycles)***					**At Recovery of Blood Counts/Assessment of Remission Status (Post-Induction Cycle 1, Post-Chemotherapy Cycle 2)/ At Relapse**	**Consolidation (up to 3 Cycles)***				**End-of-Study Treatment**	**Long-Term Follow-up** [x]
Study Visit Day [a]	-14 to 0	1	3	7	14	15 until blood count recovery		1	3	5	28 to 35	30 ± 7 days after last study treatment	
Induction therapy													
Study medication (ENTO/Placebo) [o]		→	→	→	→	→	X						
Cytarabine		→	→										
Daunorubicin or Idarubicin		→											
Consolidation therapy													
Study medication (ENTO/Placebo) [p]								→	→	→	→		
Age-adjusted, high-dose cytarabine								→	→	→			
Bone marrow evaluations													
Aspirate [q]	X						X						
NPM1-m MRD assessments [r]	X						X					X	X
Pharmacokinetics [s]		X		X	X			X			X		
Peripheral blood biomarker assessments [t]	X	X		X	X		X	X			X	X	
Bone marrow aspirate biomarker assessments [u]	X						X						
Pharmacogenomics (whole blood) [v]	X												
Patient reported outcomes [w]	X						X					X	X
Follow-up for relapse, first salvage therapy, OS [x]													X

Abbreviations: AEs, adverse events; AML, acute myeloid leukemia; β-HCG, beta human chorionic gonadotropin; ECG, electrocardiogram; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FSH, follicle stimulating hormone; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LFTs, liver function studies; MUGA, multi-gated acquisition; *NPM1*-m, *Nucleophosmin 1*-mutated; MRD, measurable residual disease; OS, overall survival.

* Subjects with ≥5% residual leukemic blasts in bone marrow aspirate between Days 14 and 28 of Induction Cycle 1 will receive Induction Cycle 2 as outlined in Table 4, which may be administered prior to blood count recovery. Subjects who have achieved a complete response (CR) either with or without full hematologic recovery (CRh, CRi) or a morphologic-free leukemia state (MFLS) will proceed to Consolidation Cycle 1 (Table 5) upon recovery of peripheral blood counts (absolute neutrophil count [ANC] ≥ 1.0 x 10^9/L; platelet count ≥ 50 x 10^9/L). After completion of Induction Cycle 2 or Consolidation Cycle 1 (ie. Chemotherapy Cycle 2), subjects will undergo bone marrow examination for assessment of remission status at the investigative site. Patients in morphologic CR post-Chemotherapy Cycle 2 will undergo MRD assessment (see footnote "r" below).

[a] Acceptable windows for study visits/assessments after C1D1 are ± 1 day; however, study treatment must be administered on the days indicated (eg, Days 1-7 for cytarabine, and Days 1-3 for daunorubicin or idarubicin in Induction Cycle 1).

[b] The following details minimally, regarding the diagnosis of AML will be collected and recorded on the eCRF: age and date of diagnosis (month, day, year); AML subtype (*de novo*; AML with myelodysplasia-related changes; therapy associated AML); history of myelodysplastic or myeloproliferative (eg, chronic myelomonocytic leukemia [CMML] syndrome; history of prior exposure to leukemogenic agents (eg. alkylating agents, topoisomerase II inhibitors); cytogenetic abnormalities identified by conventional cytogenetic testing and/or FISH; complete blood count (CBC) with differential; percent blasts (peripheral blood and bone marrow); *NPM1* mutation subtype (A, B, D, other); *FLT-3* mutational status (wild-type; internal tandem duplication [ITD] mutation, tyrosine kinase domain [TKD] mutation, or both).

[c] Vital signs include measurement of blood pressure, respiratory rate, pulse, temperature, and oxygen saturation level by pulse oximetry. After discharge from hospital, assess vital signs at each of the designated time points.

[d] Perform a complete physical examination including neurological exam at Screening. After discharge from the hospital, a targeted physical exam may be performed at each of the designated time points. Subjects ≥60 years old receiving intermediate dose cytarabine or those with impaired renal function are at risk for cerebellar toxicity. Monitor for the occurrence of nystagmus, slurred speech, or dysmetria on each day of cytarabine dosing during Induction Cycle 2 and consolidation. Follow dose modification guidelines outlined in Section 6.5.2 or in accordance with institutional care standards in the setting of neurotoxicity.

[e] Height and weight will be measured at Screening. Only weight will be measured thereafter at designated time points.

[f] ECG is required at Screening and thereafter as clinically indicated during treatment.

[g] An echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan must be performed at Screening and at the End-of-Treatment Visit. Consider repeating ECHO or MUGA within 48 hours prior to Induction Cycle 2 for subjects receiving anthracycline in Cycle 2 and at increased risk for cardiac toxicity.

[h] Record all adverse events and concomitant medications through 30 ± 7 days after treatment completion. Thereafter, record only serious adverse events assessed as study medication related.

[i] Includes hemoglobin, hematocrit, WBC and platelet counts, and WBC differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, blasts). At times not designated in Table 7, monitor CBC and WBC differential in accordance with institutional care standards until ANC is >1.0 x 10^9/L or persistent leukemia is documented. Monitor platelet counts at times designated in Table 7 and at other times, per institutional care standards until the platelet count is >100 x 10^9/L or persistent leukemia is documented. Monitor CBC and platelet count twice weekly during consolidation and at other times, as clinically indicated.

[j] Includes electrolytes (sodium, potassium, chloride, total CO_2 and/or bicarbonate, calcium, phosphate), liver function studies (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total and direct bilirubin), lactate dehydrogenase (LDH), alkaline phosphatase, blood urea nitrogen [BUN] or serum urea, creatinine, uric acid, glucose, amylase, and lipase. Include total creatine phosphokinase (CPK) at Screening, Day 14 of each induction cycle, and End of Study Treatment. At times not designated in Table 7, monitor electrolytes, LFTs, BUN, creatinine, uric acid, and phosphate in accordance with institutional care standards until the risk of tumor lysis syndrome has abated. For subjects

receiving nephrotoxic antimicrobial agents, closer monitoring of renal function throughout the period of hospitalization is recommended, consistent with institutional standards of care.

[k] Includes prothrombin time, activated partial thromboplastin time and international normalized ratio. Perform coagulation panel twice per week during Induction. For subjects with evidence of disseminated intravascular coagulation (DIC), coagulation parameters including fibrinogen should be monitored in accordance with institutional care standards until resolution**.**

[l] Includes dipstick evaluation for pH, glucose, protein, blood, leukocyte esterase and microscopic evaluation for red and white blood cells. After Screening, perform urinalysis as clinically indicated.

[m] A negative serum pregnancy test is required for female subjects (unless surgically sterile or postmenopausal) at Screening. Female subjects with medically documented ovarian failure must also have serum FSH levels within the institutional postmenopausal range at Screening. A urine pregnancy test will be performed for all females (unless surgically sterile or postmenopausal) on Day 1 of each cycle of induction and consolidation and at the End-of-Treatment Evaluation.

[n] HBV/HCV/HIV serology tests include HBsAg, anti-HBs, anti-HBc, anti-HCV, and anti-HIV.

[o] Study medication will be administered orally every 12 hours during Induction Cycles 1 and Induction Cycle 2, if administered (see Table 4**)**. Subjects are to continue receiving study medication while awaiting blood count recovery and response assessment results.

[p] Subjects who achieve CR, CRh or CRi post-Chemotherapy Cycle 2 may receive **consolidation** chemotherapy in combination with study medication (see Table 5**)**. Subjects are to continue receiving study medication while awaiting blood count recovery. The number of cycles of consolidation (up to 3) will be at the investigator's discretion.

[q] A bone marrow aspirate will be performed at Screening (within 14 days before the first administration of study treatment) for confirmation of diagnosis, morphology (spicule prep), cytogenetics/FISH and *NPM1* and *FLT-3* mutational status. **In cases in which an adequate bone marrow aspirate cannot be obtained at Screening (eg, due to dry tap, hypocellularity or hemodilution), a trephine bone marrow biopsy is mandated**. Bone marrow aspirates are required in Induction Cycle 1 (up to but no later than Day 42) and again post-Chemotherapy Cycle 2 (no later than Day 42) to assess remission status. Thereafter, perform bone marrow examination for confirmation of suspected leukemic relapse.

[r] *NPM1*-m allelic frequency will be assessed in peripheral blood and bone marrow aspirate in a central laboratory at the following time points: Screening; post-Chemotherapy Cycle 2 for subjects in CR (no later than Day 42, **for MRD assessment**); and at the End of Study Treatment visit (***peripheral blood only***). MRD will be assessed retrospectively on peripheral blood in subjects who achieve MRD negative CR post-Chemotherapy Cycle 2, every 3 months during long term follow-up until morphologic relapse.

[s] Blood sampling for pharmacokinetic assessments will be performed at the following time points: **Cycle 1 (Induction):** Day 1 between 2- and 4-hours post-study medication dose, Day 7 predose only, Day 14 predose and between 2- and 4-hours post-study medication dose; **Cycle 3 (Consolidation):** Day 1 predose and between 2- and 4-hours post-study medication dose, Day 28-35 predose and between 2- and 4-hours post-study medication dose. All predose samples must be obtained within 60 minutes before the first daily dose of study medication (Section 8.7).

[t] Blood samples for biomarker assessments including (but not limited to) other somatic mutations will be obtained at Screening; **Cycle 1 (Induction)**, Day 1 (predose and 2 hours post-dose), Day 7 and Day 14 (predose only) prior to the first daily dose of study medication; **Cycle 3 (Consolidation)** Day 1 (predose) and Day 28-35 (predose); at time of post-Chemotherapy Cycle 2; relapse; and End of Study Treatment. See Section 8.9 for a description of planned biomarker assessments.

[u] Bone marrow aspirate samples for biomarker assessments including (but not limited to) other somatic mutations will be obtained at Screening; post-Chemotherapy Cycle 2; and at relapse.

[v] Whole blood will be collected during Screening for evaluation of CYP2C9 and cytidine deaminase polymorphisms. Examinations of other germline genes implicated in leukemogenesis may be conducted for comparison with corresponding genes in the leukemic clone. See Section 8.9 for additional details.

[w] Includes the European Quality of Life 5 Dimensions Questionnaire (EQ-5D-5L) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ 30).

[x] All subjects regardless of post-remission status will be followed monthly for 3 months after the End-of-Treatment Visit and thereafter at least once every 3 months for progression/relapse, first salvage therapy, and overall survival until study termination.

8.1 Informed Consent

Study site personnel must obtain signed informed consent before any study-specific procedures (including central laboratory screening for the presence of *NPM1* and *FLT3* mutations) are conducted unless these are part of the standard of care and must document the informed consent process in the patient's medical record. Consent must be obtained using the most current version of ICF approved by the study site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Once the patient signs the ICF, that will signal the beginning of the 14-day Screening Period. Selected screening assessments may be repeated once for final eligibility determination if thought to be out-of-range due to artifact or transient abnormality. These include the following: ECG, ECHO, clinical chemistries/liver function studies, coagulation screening studies and HBV/HCV/HIV serologies.

8.2 Confirmation of Eligibility

All screening assessments and relevant medical history must be available and reviewed by the investigator before eligibility can be confirmed. Eligibility waivers will not be granted. After the investigator determines that a patient is eligible, study site personnel will complete an enrollment authorization form to be sent to the medical monitor for review/approval. Written authorization by the medical monitor is required before a patient can be officially enrolled and begin study treatment.

8.3 Medical and Leukemia History

Clinically significant medical and surgical history not pertaining to the underlying malignancy under study that started prior to informed consent will be collected. "Clinically significant" is generally regarded as any diagnosis requiring on-going treatment intervention and follow-up. Signs and symptoms of concurrent medical conditions must be adequately documented at Screening in order to establish baseline severities. Clinically relevant prior and current medical and surgical history will be reported on the Medical and Surgical History eCRF.

Smoking history (never smoker; former smoker; current smoker) will also be recorded.

The following details minimally regarding the diagnosis of AML will be collected and recorded on the eCRF: age and date of diagnosis (month, day, year); AML subtype (*de novo*; AML with myelodysplasia-related changes; therapy associated AML); history of myelodysplastic or myeloproliferative (eg, chronic myelomonocytic leukemia [CMML]) syndrome; history of prior exposure to leukemogenic agents (eg. alkylating agents, topoisomerase II inhibitors); cytogenetic abnormalities identified by conventional cytogenetic testing and/or FISH; CBC with differential; percent leukemic blasts (peripheral blood and bone marrow); *NPM1* mutation subtype (A, B, D, other); *FLT-3* mutational status (wild-type; internal tandem duplication [ITD] mutation, tyrosine kinase domain [TKD] mutation, or both).

8.4 Study Medication Dispensation

During periods of hospitalization, study medication (ENTO or placebo) will be dispensed by the in-patient pharmacy and administered by in-patient medical/nursing staff. Study medication for

outpatient use will be dispensed by study center personnel to ensure adequate drug supply for home administration throughout the treatment phase in accordance with details outlined in the Pharmacy Manual. Instructions will be provided to subjects for dosing, storage, and disposition of unused study drug.

8.5 Efficacy Assessments

Assessments that define the quality of response to study treatment will include physical examination, peripheral blood counts, and bone marrow examination. All assessments of response will be made by the investigator in accordance with ELN 2017 criteria (Döhner 2017) with minor modification for neutrophil and platelet count thresholds that define CR per the International Working Group (IWG) criteria (Cheson 2003). See Appendix 4 for criteria that define each response category.

8.5.1 Bone Marrow Examination

A bone marrow aspirate will be performed at Screening (within 14 days before the first administration of study treatment) for confirmation of diagnosis, morphology (spicule prep), cytogenetics/FISH and *NPM1* and *FLT3* mutational status. **In cases in which an adequate bone marrow aspirate cannot be obtained at Screening (eg, due to dry tap, hypocellularity or hemodilution), a trephine bone marrow biopsy is mandated**. Bone marrow aspirates are required in Induction Cycle 1 (up to but no later than Day 42) and again post-Chemotherapy Cycle 2 (no later than Day 42) to assess remission status. Thereafter, perform bone marrow examination for confirmation of suspected leukemic relapse.

Additional biomarker assessments including (but not limited to) the presence of other somatic mutations at each of the aforementioned timepoints will be conducted (see Section 8.8).

8.5.2 Measurable Residual Disease

NPM1-m MRD assessments on peripheral blood and bone marrow aspirate will be conducted in a central laboratory post-Chemotherapy Cycle 2 for subjects in CR, no later than Day 42. Additionally, *NPM1*-m will be assessed as part of a broader panel of AML somatic mutations on peripheral blood only at End of Study Treatment, and every 3 months during long term follow-up in subjects who achieve MRD negative CR post-Chemotherapy Cycle 2, until morphologic relapse.

8.6 Safety Assessments

8.6.1 Physical Examination and Vital Signs

A complete physical examination that includes a neurological exam must be performed at Screening. Thereafter, a targeted physical exam may be performed at each of the designated time points in Table 7. Height and weight will be measured at Screening. Only weight will be measured thereafter at designated time points.

Vital signs include measurement of blood pressure, respiratory rate, pulse, temperature, and percent oxygen saturation by pulse oximetry. After discharge from hospital, assess vital signs at each of the designated time points indicated in Table 7.

Blood pressure and pulse should be measured at least 5 minutes after rest in a quiet setting without distractions. To the extent possible, measure vital signs prior to blood collection for laboratory assessments.

Subjects ≥ 60 years of age or those with impaired renal function receiving cytarabine at doses specified in this study are at risk for cerebellar toxicity. Monitor for the occurrence of nystagmus, slurred speech, or dysmetria on each day of cytarabine dosing during induction and consolidation. Follow dose modification guidelines outlined in Section 6.5.2 or those consistent with institutional care standards in the setting of neurotoxicity.

8.6.2 Electrocardiogram

A triplicate, 12-lead ECG will be obtained as outlined in Table 7. ECG is required at Screening and thereafter as clinically indicated during treatment.

8.6.3 Echocardiography/Multi-gated Acquisition Scan

An echocardiogram (ECHO) or multigated acquisition (MUGA) scan must be performed at Screening and at the End-of-Treatment Visit. For subjects receiving anthracycline in Induction Cycle 2, consider repeating an ECHO or MUGA scan within 48 hours prior to Cycle 2, Day 1 in subjects at increased risk for cardiotoxicity.

8.6.4 Laboratory Assessments

See Table 7 for the list of clinical laboratory tests to be performed and their timing and frequency.

The investigator must review results for protocol-specified laboratory assessments, document his/her review, and record any clinically significant changes from baseline, defined as the value most proximate to initiation of study treatment, as an AE. If laboratory abnormalities from non-protocol specified laboratory tests require a change in subject management or are considered clinically significant (eg, requiring treatment modification), these must also be recorded as an AE. Laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the underlying condition. Clinically significant laboratory abnormalities should be reassessed during the study, up to 30 days after the last dose of study treatment until the results return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If clinically significant abnormalities do not return to normal/baseline within a time period judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.

Hematology:

Includes hemoglobin, hematocrit, white blood cell (WBC) and platelet counts, and WBC differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, blasts). At times not designated in Table 7, monitor CBC and WBC differential in accordance with institutional care

standards until ANC is >1.0 x 10^9/L or persistent leukemia is documented. Monitor platelet counts at times designated in Table 7 and at other times, per institutional care standards until the platelet count is >100 x 10^9/L or persistent leukemia is documented. Monitor CBC and platelet count twice weekly during consolidation and at other times, as clinically indicated.

Clinical Chemistries:

Includes electrolytes (sodium, potassium, chloride, total CO_2 and/or bicarbonate, calcium, phosphate), liver function studies (AST, ALT, total and direct bilirubin), lactate dehydrogenase, alkaline phosphatase, blood urea nitrogen (BUN) or serum urea, creatinine, uric acid, glucose, amylase, and lipase. Include total creatine phosphokinase at Screening, Day 14 of each Induction cycle, and at the End of Study Treatment. At times not designated in Table 7, monitor electrolytes, LFTs, BUN, creatinine, uric acid, and phosphate in accordance with institutional care standards until the risk of tumor lysis syndrome has abated. For subjects receiving nephrotoxic antimicrobial agents, closer monitoring of renal function throughout the period of hospitalization is recommended, consistent with institutional standards of care.

Coagulation Parameters:

Includes prothrombin time, activated partial thromboplastin time and international normalized ratio. Perform coagulation panel twice per week during induction. For subjects with evidence of disseminated intravascular coagulation, coagulation parameters including fibrinogen should be monitored until resolution.

Hepatitis/HIV Serologies:

Includes HBsAg, anti-HBs, anti-HBc, anti-HCV, and anti-HIV. Patients who are seropositive for HBsAg are excluded. HIV + patients may be considered for enrollment if they meet all criteria outlined in Section 5.2 and for whom the risk of adverse interactions between anti-retroviral therapy and the study medication is assessed as minimal to none.

Urinalysis:

Includes dipstick evaluation for pH, glucose, protein, blood, leukocyte esterase and microscopic evaluation for red and white blood cells. After Screening, perform urinalysis as clinically indicated.

8.6.5 Pregnancy testing

A negative serum pregnancy test is required for female subjects (unless surgically sterile or postmenopausal) at Screening. Female subjects with medically documented ovarian failure must also have serum follicle stimulating hormone (FSH) levels within the institutional postmenopausal range at Screening. A urine pregnancy test will be performed for all females (unless surgically sterile or postmenopausal) on Day 1 of each cycle of induction and consolidation and at the End-of-Treatment evaluation.

8.7 Pharmacokinetic Assessments

Whole blood will be collected for measurement of plasma concentrations of ENTO at the following time points using a validated liquid chromatography mass spectrometry (LC-MS/MS) method:

Cycle 1 (Induction):

- Day 1, between 2 and 4 hours after study medication dose
- Day 7 predose only
- Day 14 predose and between 2 and 4 hours after study medication dose

Cycle 3 (Consolidation):

- Day 1 predose and between 2 and 4 hours after study medication dose
- Day 28-35 predose and between 2 and 4 hours after study medication dose

All predose samples must be obtained within 60 minutes before the first daily dose of study medication. The actual date and time (24-hour clock time) of each blood draw will be recorded.

Details concerning the processing and handling of PK samples, including labeling and shipping instructions will be provided in the Laboratory Manual.

8.8 Biomarker Assessments

Whole blood for biomarker testing will be obtained at the following time points:

- Screening,
- **Cycle 1** (**Induction)**, Day 1 (pre- and 2 hours postdose), Day 7 and Day 14 (predose),
- Post-Chemotherapy Cycle 2
- **Cycle 3** (**Consolidation)**, Day 1 (predose) and Days 28-35 (predose),
- At relapse, and
- End of Study Treatment.

All predose samples must be obtained within 60 minutes before the first daily dose of study medication. The actual date and time (24-hour clock time) of each blood draw will be recorded.

The extent of ENTO target engagement as measured by quantitation of pSYK and other phosphoproteins of interest as well as expression levels of relevant genes comparing baseline and on treatment blood samples will be explored. Additional targeted protein/phosphoprotein profiling (eg, pSYK expression) in leukemic cells specifically will be assessed at baseline. Biomarker assessments will also include baseline expression levels of *HOXA9/MEIS1* transcription factors and other relevant genes in leukemic cells from peripheral blood and bone marrow aspirate using standard expression profiling platforms (eg, Nanostring®) or next-generation sequencing. Mutational profiling in leukemic cells using standard platforms like next generation sequencing both at baseline and following study treatment will be explored. Results of all biomarker assessments will be evaluated for potential correlations with response and leukemic progression.

Details concerning the processing and handling of biomarker samples, including labeling and shipping instructions will be provided in the Laboratory Manual.

8.9 Pharmacogenomic Assessments

A whole blood sample will be collected at Screening for assessments of CYP2C9 and cytidine deaminase (the enzyme primarily responsible for cytarabine metabolism) polymorphisms. CYP2C9 polymorphisms will be evaluated in relationship to ENTO exposures (AUC, C_{max}) and as a potential covariate in population PK analyses. Cytidine deaminase polymorphisms will be evaluated for potential correlations with selected safety and efficacy outcomes. Examinations of selected germline genes implicated in leukemogenesis may be conducted for comparison with the corresponding genes in the leukemic clone.

8.10 Patient Reported Outcomes

Includes the European Quality of Life 5 Dimensions Questionnaire (EQ-5D-5L) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ 30) collected at baseline, post-Chemotherapy Cycle 2, at End-of-Treatment and every 3 months thereafter until progression/relapse or death (whichever is earlier).

8.11 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

Definitions for AEs and SAEs as well as methods for evaluating and reporting AEs and SAEs can be found in Appendix 2.

8.11.1 Time Period for Reporting AEs and SAEs

During the period from signing informed consent for this study until initiation of study treatment, only SAEs will be reported. Beginning on Day 1 of Cycle 1 all AEs, and SAEs will be reported through 30 days after treatment completion. Thereafter, only SAEs that are study medication related as assessed by the investigator will be reported.

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities are met. All SAEs will be reported to the sponsor or designee immediately, without undue delay, as outlined in Appendix 2. The investigator will submit any updated SAE data to the sponsor immediately, without undue delay.

8.11.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when eliciting information on the occurrence of AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AEs. Investigators are not obligated to actively seek information on AEs or SAEs after the End-of-Treatment evaluation. However, if the investigator learns of any SAE, including a death, at any time after a subject has discontinued study treatment, and he/she considers the event to be reasonably related to the study medication or study participation, he/she must promptly notify the sponsor.

8.11.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs, including SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 2.

8.11.4 Regulatory Reporting Requirements for SAEs

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study medication under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to regulatory authorities, IRB/IEC, and investigators.

Investigators who receive a safety report describing an SAE or other safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it with the applicable reference safety information and will notify the IRB/IEC, if appropriate, according to local requirements. For this study, the reference safety information for the study medication, ENTO, is the Investigator's Brochure (Edition 11.0). For all chemotherapy agents (cytarabine, daunorubicin, idarubicin), the reference safety information is the local health authority-approved prescribing information.

Safety reports must be prepared for SUSARs in accordance with local regulatory requirements and Sponsor policy and forwarded to study investigators, as necessary.

8.11.5 Reporting Pregnancy

If a female patient or the partner of a male patient becomes pregnant while receiving or within 3 months of discontinuing study treatment, a pregnancy report form must be completed and submitted to the sponsor within 24 hours of learning of the pregnancy (after obtaining the necessary signed informed consent from the female partner of a male patient) to facilitate outcomes follow-up.

While pregnancy itself is not considered an AE, any pregnancy complications (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or elective termination of a pregnancy for medical reasons will be reported as a SAE. For pregnancies taken to term, details on the status of the mother and the child will be forwarded to the sponsor, with follow-up generally no longer than 6 to 8 weeks after the delivery date. Any female participant who becomes pregnant while participating in the study will discontinue study treatment but may continue to be followed for leukemic progression/relapse, first salvage therapy and survival.

Any post-study pregnancy-related SAE considered by the investigator at least possibly related to the study treatment will be reported to the Sponsor as described in Section 8.11.4. While the investigator is not obligated to actively seek this information from former study subjects or pregnant female partners of male subjects, he or she may learn of an SAE through spontaneous reporting.

9.0 Statistical Considerations

9.1 Statistical Hypotheses

The primary efficacy endpoint is MRD negative CR rate after Chemotherapy Cycle 2.

The hypothesis of interest is a two-sided test of superiority comparing ENTO to placebo.

$$H_0: p_{placebo} = p_{ENTO} \text{ vs } H_{11}: p_{placebo} \neq p_{ENTO},$$

where $p_{placebo}$ is the proportion of subjects in the placebo group with MRD negative CR after Chemotherapy Cycle 2, and p_{ENTO} is the proportion of subjects in the ENTO group with MRD negative CR after Chemotherapy Cycle 2.

9.2 Sample Size Determination

Based on a completed study of newly diagnosed AML subjects treated with ENTO, it is anticipated that 87% of *NPM1*-m subjects will achieve CR (Walker 2020). Based on analysis of a historical dataset from the Cancer and Leukemia Group B Alliance (Mims et al, 2021) showing a 68% CR rate in 107 *NPM1*-mutated/*FLT3-ITD* negative patients ≥ 60 years of age treated with 7+3 induction, a conservative estimate of 70% CR rate for placebo is assumed for sample size determination. The MRD negative rate among placebo subjects achieving CR is assumed to be 60% (Ivey et al, 2016). Alternatively, it is hypothesized that 80% of subjects with CR receiving ENTO will be MRD negative. A sample size of 90 subjects per group (total of 180 subjects) will provide > 97% power to detect a difference in the MRD negative CR rate of 28% (87% x 80% = 70% for ENTO vs 70% x 60% = 42% for placebo) with a 2-sided alpha level of 0.05 (PASS 2008: Two sample test of Proportion Module). Up to 10% over enrollment is allowable in order to account for technical or logistical barriers (eg. inadequate bone marrow aspirate or poor sample quality) related to the ascertainment of MRD status in patients who achieve CR post-Chemotherapy Cycle 2.

Assuming the two-year EFS rate for the control group is 63% (hazard rate of 0.231), a total of 124 events (70 in the placebo arm, 54 in the ENTO arm) would be sufficient to provide 80% power to detect a hazard ratio of 0.6 for EFS (PASS 2008: log rank tests (Lakatos) [Hazard Rate] module) assuming 2-sided alpha = 0.05 and a total study duration of 60 months.

9.3 Analysis Sets

Population	Definition
Intent-to-Treat Analysis Set	All subjects randomized.
Safety Analysis Set	All subjects randomized who receive at least one dose of study medication.
PK Analysis Set	All subjects with at least 1 ENTO plasma concentration
Biomarker Analysis Set	All subjects with at least 1 biomarker assessment result

9.4 Statistical Analyses

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). Described below is a summary of the planned statistical analyses of the primary and key secondary endpoints.

9.4.1 General Considerations

Summary statistics and listings will be used to analyze the study data. Continuous variables will be summarized by means, standard deviations, medians, interquartile ranges, minimal and maximal values. Categorical variables will be summarized by number and percentage. Any statistical testing will be conducted at the alpha = 0.05 level (2-sided).

Unless otherwise specified, data summaries and analyses described below will be reported by treatment group.

9.4.2 Primary Endpoint

Measurable Residual Disease Negative Complete Response

The primary efficacy endpoint is the proportion of subjects who achieve CR without MRD (MRD negative [<0.01%] CR rate) Post-Chemotherapy Cycle 2 as defined by the absence of *NPM1*-m alleles in bone marrow aspirate based on a molecular assay (eg, next generation sequencing) in a central reference laboratory designated by the Sponsor.

9.4.2.1 Statement of Estimand

The **population for the trial** is defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval, adults with previously untreated *NPM1*-m AML who are candidates for intensive induction/consolidation chemotherapy. The analysis population is based on the Intent-to-treat Analysis set and includes subjects who have been randomized.

The **treatments** of interest are ENTO or placebo in combination with intensive induction and consolidation chemotherapy.

The **variable** of interest is the MRD negative CR rate post-Chemotherapy Cycle 2.

The ability to evaluate treatment effect using the variable may be impacted by **intercurrent events.** Death, use of additional leukemic treatments, and premature discontinuation of study drug may all impact the interpretation of treatment effect. Given that death equates to a poor outcome, a composite strategy will be implemented including all available data through the evaluation of response post-Chemotherapy Cycle 2; subjects who die before the end of Chemotherapy Cycle 2 will be considered as not having achieved MRD negative CR.

The **population level summary measure** is the risk difference (difference in the proportion of subjects with MRD negative CR Post-Chemotherapy Cycle 2).

9.4.2.2 Primary Endpoint Analysis

The primary evaluation of the primary analysis endpoint will be conducted utilizing the estimand as described in Section 9.4.2.1. Subjects with a missing evaluation of MRD post-Chemotherapy Cycle 2 will be imputed as failures for the analysis. Additional information on the handling of missing data, planned sensitivity measures, and supportive analyses will be detailed in the SAP.

Risk difference will be estimated using stratum-adjusted Mantel-Haenszel proportions, and 95% confidence intervals around the treatment difference will be calculated. The differences are weighted by the harmonic mean of the sample size in each treatment group per stratum (age < 60 vs ≥ 60 years; daunorubicin vs idarubicin anthracycline). If n_{1h} and n_{2h} are the sample sizes of the two treatment groups for a given comparison, say treatment groups 1 and 2, in any given stratum, called stratum h, then the weight in stratum h is given by,

$$w_h = \frac{n_{1h} n_{2h}}{n_{1h} + n_{2h}}$$

Let $d_h = p_{1h} - p_{2h}$ be the difference in the proportion of subjects with MRD negative CR in treatment group 1 and treatment group 2 in stratum h. The stratum-adjusted Mantel-Haenszel proportion is given by,

$$d = \frac{\sum_h w_h d_h}{\sum_h w_h}$$

The continuity corrected variance is given by,

$$\text{var} = \frac{\sum_h w_h^2 \left(\frac{p_{1h}^* \left(1 - p_{1h}^*\right)}{n_{1h} - 1} + \frac{p_{2h}^* \left(1 - p_{2h}^*\right)}{n_{2h} - 1} \right)}{\left(\sum_h w_h \right)^2}$$

where $p_{1h}^* = \frac{m_{1h} + 0.5}{n_{1h} + 1}$, $p_{2h}^* = \frac{m_{2h} + 0.5}{n_{2h} + 1}$, m_{1h} and m_{2h} are the number of subjects with MRD negative CR in treatment groups 1 and 2, respectively.

9.4.3 Secondary Endpoint(s)

The secondary endpoint variables and their population level summary measures will be described in each of the following sections. The evaluation of the population for the trial, treatments of interest, and the possible intercurrent events are as described in Section 9.4.2.1. All secondary endpoints will include death as part of definition of the variable. Intercurrent events of additional leukemic therapy and premature study treatment discontinuation will be ignored for the primary evaluation of these endpoints. Additional information on the handling of missing data and sensitivity analyses will be detailed in the SAP.

Event-free survival

Event-free survival (EFS) is defined as time from randomization to the earliest of induction treatment failure (ITF), relapse for those who achieve CR, or death from any cause. ITF is failure to achieve morphological CR after completion of the last cycle of induction chemotherapy (no later than Day 42 of the last cycle of induction). Subjects who experience ITF will be treated as events at Day 1.

Subjects who do not experience an event (ITF, relapse from CR, or death) will be censored at their last study evaluation at which they were relapse free. Event-free survival will be estimated using the method of Kaplan-Meier (K-M) and summarized by treatment group. Differences between the treatment groups will be assessed with the log rank test stratified by age (<60 vs ≥60 years) and choice of anthracycline in induction (daunorubicin vs idarubicin). The population level summary measure will be the adjusted hazard ratio as calculated from a Cox proportional hazards model with effects for treatment, age, and choice of anthracycline in induction.

Relapse free survival

For subjects who achieve CR, relapse free survival (RFS) is defined as the time from CR to morphologic relapse as assessed by the study site investigator or death from any cause, whichever comes first. Subjects who do not experience a relapse or death will be censored at the last study evaluation at which they were relapse free. RFS will be estimated using the K-M method and summarized by treatment group. The population level summary measure will be the adjusted hazard ratio as calculated from a Cox proportional hazards model with effects for treatment, age, and choice of anthracycline in induction.

Overall survival

Overall survival is defined as the time from randomization to death from any cause. Subjects who are alive at last contact will be censored at their date of last contact. Overall survival will be estimated using the K-M method and summarized by treatment group. Differences between the treatment groups will be assessed with the log rank test stratified by age (< 60 vs ≥ 60 years) and choice of anthracycline in induction (daunorubicin vs idarubicin). The population level summary measure will be the adjusted hazard ratio as calculated from a Cox proportional hazards model with effects for treatment, age, and choice of anthracycline in induction.

Categorical secondary endpoints will be analyzed similarly to the primary efficacy endpoint, and other time-to-event secondary endpoints will be analyzed similarly to EFS. To avoid inflation of Type I error for the secondary endpoints, statistical comparisons will be made at the time of the confirmatory analysis using a hierarchical approach with EFS tested first followed by RFS, and then overall survival. Details of the hierarchical analysis will be provided in the SAP.

9.4.4 Safety Analysis

All safety analyses will be conducted on the Safety Analysis Set.

Treatment-emergent adverse events (TEAEs) defined as all events beginning or worsening from Cycle 1, Day 1 through 30 days following study treatment completion, will be coded according to the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) and will

be summarized by treatment group, system organ class, and preferred term. Unless otherwise specified, only TEAEs will be reported in safety summaries and listings.

Additional summaries by seriousness, severity, causality, and outcomes will also be prepared. Adverse events leading to ENTO dose reduction or discontinuation as well as those with an outcome of death will be summarized with descriptive statistics. Changes from baseline in selected laboratory assessments of interest will be summarized by treatment group and severity grade.

9.5 Timing of Analyses

9.5.1 Data Monitoring Committee

An independent DMC, consisting of two expert hematologists and one expert biostatistician will monitor emerging safety and efficacy data from this trial on an ongoing basis. The DMC will provide a suitable recommendation to the Sponsor for appropriate study direction. Such direction may include continuation of the trial as planned, modification of study conduct/design or early termination based on safety or futility. A DMC charter delineates the responsibilities of the DMC and its interactions with other trial components. Data monitoring committee analyses will be focused on safety and efficacy endpoints and will be conducted regularly as outlined in the DMC charter.

9.5.2 Blinded Review of EFS Events

Prior to unblinding for the primary endpoint analysis, the sponsor will review the number of EFS events achieved. If the rate of events is slower than anticipated, the sponsor may propose an increase in sample size in order to achieve the events necessary for the confirmatory analysis of EFS. The increase will be based on the original sample size assumptions for hazard ratio and two-year EFS rate of the placebo group. The proposed sample size increase will be shared with the DMC and appropriate regulatory agency prior to implementation. Given that the review will be conducted in a blinded fashion, no adjustment for Type 1 error is proposed.

9.5.3 Primary Endpoint Analysis

The primary endpoint analysis will be conducted once 180 subjects complete Chemotherapy Cycle 2 (or discontinue study participation prior to the assessment) and the resulting database is cleaned and locked.

9.5.4 EFS Analysis

A final EFS analysis will be conducted once the pre-specified number of events have been reported and the resulting database is cleaned and locked.

10.0 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The protocol and protocol amendments will be submitted to the regulatory agencies by the Sponsor, as applicable.
- The protocol and any substantial amendments to the protocol will require health authority approval prior to initiation, where applicable, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators are required to provide the sponsor with complete and accurate financial information in accordance with regulations to allow the sponsor to submit disclosure or certification of the absence of certain financial interest or to disclose those financial interests as required, to the appropriate health authorities. This is to ensure that financial interests and arrangements between

clinical investigators and Kronos Bio, which could affect the reliability of data submitted to health authorities, are identified, and disclosed. Investigators are responsible for providing information about their financial interests before their participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

The investigator is responsible for obtaining written, informed consent from each prospective study subject using the IRB/IEC-approved consent form, after adequately explaining the objectives, methods, and potential hazards of study participation and before conducting study-related procedures or assessments. Each informed consent form will be signed and dated by the subject or, where permissible by local laws and regulations, the subject's legally authorized representative and the person obtaining consent.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) must be provided to the subject or their legally authorized representative. The process of obtaining informed consent and contents of the informed consent form will be in accordance with the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

If a subject chooses to withdraw from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before withdrawal of consent.

10.1.4 Data Protection

Subjects will be assigned a unique identifier by the Sponsor. Any subject's records or datasets that are transferred to the Sponsor will contain the identifier only; subject's names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, appropriate IRB/IEC members, and inspectors from regulatory agencies.

10.1.5 Dissemination of Clinical Study Data

A clinical study report will be prepared detailing the outcomes of this study and provided to regulatory authorities including the US FDA and others, as applicable. Kronos Bio will ensure that this report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Results from this study will be published or presented at scientific meetings in a timely and objective manner regardless of the outcome of the study in a manner consistent with good science, industry and regulatory guidance, and in accordance with the terms of the applicable clinical study agreement. Data generated in this clinical study are the exclusive property of the sponsor and will remain confidential until such time as they are publicly disclosed. As this is a multicenter study, the first publication or disclosure of study results shall be a joint, multicenter publication or disclosure coordinated by the sponsor or its designee. Thereafter, any secondary publications will reference the first (original) publication. Authorship shall be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for manuscripts or alternatively, stricter local criteria (International Committee of Medical Journal Editors, 2013).

No communication, presentation or publication will include Kronos Bio's confidential information.

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor prior to submission for peer-review or presentation in accordance with the terms outlined in the clinical study agreement. This will allow the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator and ensure scientific and clinical accuracy. The procedure for reviewing manuscripts and presentations that are based on results from this study is detailed in the investigator's clinical study agreement. Each investigator acknowledges and agrees that in accordance with the clinical study agreement, a delay in publication/presentation may be requested by the sponsor to allow for patent filings in advance of the latter or deletion of sponsor's confidential information.

10.1.6 Data Quality Assurance

Data required by the study protocol will be entered into eCRFs in an EDC system that is compliant with all regulatory requirements. All study-related data collected or received by the investigator or study team shall be promptly entered into the eCRFs after the data is collected or received by the investigator or study team in a time frame consistent with what is stipulated in the study site contract.

Data recording onto eCRFs must follow the data entry instructions provided in the eCRF completion guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data. The investigator or his/her designee in the "Statement of Investigator Form" at the front of this protocol must sign the completed casebooks to attest to their accuracy, authenticity, and completeness.

All final patient data recorded onto eCRFs as well as external data (eg, central laboratory assessments) collected in accordance with this protocol will be stored at Kronos Bio or a designated off-site facility at the end of the study. Data will be reviewed for the presence of potential outliers or inconsistencies as well as for logic and completeness. Standard procedures including data review guidelines, computerized validation for query generation and maintenance of an audit file that includes database modifications will be followed to ensure accurate data collection.

10.1.7 Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. During the course of the study, a study monitor will make regular visits to the study site or engage with the study site via videoconference or through other digital media to review protocol compliance, compare data entered onto eCRFs with individual study subjects' medical records (ie, source data verification) and ensure that the study is being conducted in accordance with pertinent regulatory requirements. The source data verification process will be conducted in a manner to ensure that the confidentiality of study subjects is maintained. Direct access to source data will also be required for inspections and audits and be carried out with due consideration to data protection and confidentiality.

10.1.8 Study/Site Termination

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

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

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

For study termination:

- Discontinuation of all evaluation of the study's objectives and endpoints.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the investigator
- Total number of subjects enrolled is earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform study subjects and assure the availability of appropriate therapy and/or follow-up.

10.1.9 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

10.2 Appendix 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline and considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of the underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug- drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Progression or relapse of leukemia should not be reported as an AE. Signs, symptoms or other clinical sequelae of leukemic progression/relapse should be reported (eg, worsening/recurrence of cytopenias/peripheral blast counts; bleeding; infection; new or worsening extramedullary disease) should be reported as such on the AE eCRF).
- Death is an outcome and not usually considered an event. For example, in the case of overwhelming sepsis leading to death, "overwhelming sepsis (Grade 5)" would be recorded as the event with death as the outcome. If the cause of death is unknown, the death is then reported as an event (ie, "death due to unknown cause" or "death unexplained").

10.2.2 Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of study treatment dependency or abuse.

A suspected, unexpected serious adverse reaction (SUSAR) is a serious adverse event that is both unexpected (ie, not listed in the Reference Safety Information for the investigational agent) and meets the definition of an adverse drug reaction, the specificity or severity of which is not consistent with those noted in the Reference Safety Information (ie, the Investigator's Brochure for an investigational agent).

10.2.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information onto study specific data collection tools (eg, AE eCRF log, SAE report form).
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the sponsor in lieu of completion of the required reporting form.
- There may be instances when copies of medical records for certain cases are requested by sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of severity for each AE reported during the study. AEs should be assessed and graded for severity based on the NCI-CTCAE v. 5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

Toxicities that are not specified in the NCI-CTCAE will be graded for severity as follows:

- Grade 1 (Mild): Asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated
- Grade 2 (Moderate): Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3 (Severe): Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4 (Life-threatening): Urgent intervention indicated required to remove or abrogate risk of death
- Grade 5: Death related to AE

Note: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (as characterized above) whereas seriousness as defined above, defines the requirements for reporting obligations from the sponsor to applicable regulatory authorities.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor or its designee. Investigators must always make an assessment of causality for every event before transmission of the initial SAE report to the Sponsor/designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- After an initial AE or serious AE is reported, those that are designated as ongoing from a previous visit/contact must be reviewed at subsequent visits.
- All adverse events will be followed until resolution, stabilized or considered chronic, or the study participant is either lost to follow-up or withdraws consent.
- The investigator will ensure that follow-up reporting includes any supplemental investigations that were obtained to further elucidate the nature and/or causality of the event, including additional laboratory or radiographic evaluations, histopathologic examination or consultation with other health care professionals.
- The sponsor may request that the investigator perform or arrange for the conduct of supplemental evaluations to elucidate as fully as possible the nature and/or causality of any event.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor immediately, without undue delay.
- If a study participant dies while on study or during a pre-specified follow-up period, the sponsor will be provided with a redacted copy of any postmortem findings, including histopathologic findings.

10.2.4 Reporting of SAEs

SAE Reporting to Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event immediately, without undue delay.
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form (see next section) or to the sponsor/medical monitor by telephone.
- Contacts for SAE reporting can be found in the eCRF completion guidelines.

SAE Reporting to Sponsor via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the sponsor/medical monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found on the paper SAE form.

10.3 Appendix 3: Contraceptive and Barrier Guidance

10.3.1 Definitions

Women in the following categories are <u>not</u> considered Women of Childbearing potential (WOCBP)

1. Premenopausal female with one of the following:
   - Documented hysterectomy.
   - Documented bilateral salpingectomy.
   - Documented bilateral oophorectomy.

   Documentation can come from a review of the patient's medical records, medical examination, or medical history interview.

2. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.3.2 Contraception Guidance

Male subjects

Male subjects with female partners of child-bearing potential are eligible to participate if they agree to the following during the study:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinence on a long term and persistent basis) and agree to remain abstinent for the duration of study and for at least 3 months after the last dose of study medication.
- Female partner is using a highly effective contraceptive method, including one of the highly effective contraceptives listed in the table below.
- Agree to use a male condom.
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a condom during the study.
- Refrain from donating sperm for the duration of study and for at least 3 months after the last dose of study medication.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly,*[a]
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.[b] • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation.[b] • Oral • Injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

b) Based on current knowledge, drug-drug interactions are not expected between ENTO and hormonal contraceptives that could potentially reduce their effectiveness in pregnancy prevention. Nevertheless, WOCBP using one of the highly effective, hormonal contraceptives described above (either birth control pills or implantable devices) will be required to also employ a barrier method of contraception (eg. condom use by a male partner, diaphragm, or cervical cap) for at least 3 months after the last dose of study treatment.

Female subjects

Female subjects of reproductive potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table above in combination with a barrier method (eg, condom use by a male partner, diaphragm, or cervical cap), as noted above.

10.3.3 Pregnancy Testing

WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at Screening and a negative urine pregnancy test on Day 1 of each cycle of induction and consolidation and at the End-of-Treatment Evaluation.

10.3.3.1 Collection of Pregnancy Information

Male subjects with partners of reproductive potential who become pregnant

- The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor or designee within 24 hours of learning of the partner's pregnancy.
- The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor or designee.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female subjects who become pregnant

- The investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to the sponsor or designee within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on the subject and the neonate, which will be forwarded to the sponsor or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy that is considered reasonably related to the study treatment by the investigator, will be reported to the sponsor or designee. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will discontinue study treatment but may continue to be followed for leukemic progression/relapse, first salvage therapy and survival. Further treatment options will be discussed.

10.4 Appendix 4: Response Criteria

Complete Response (CR)*

CR requires all the following:

- Bone marrow blasts < 5%
- Absence of circulating blasts and blasts with Auer rods
- Absence of extramedullary disease (ie, leukemia outside of bone marrow confirmed by biopsy)
- Absolute neutrophil count > 1.0 x 10^9/L (1000/μL)
- Platelet count > 100 x 10^9/L (100,000/μL)

*Note: *MRD positive or unknown*

Complete Response with Hematologic Improvement (CRh)**

CRh requires all the CR criteria, except for residual thrombocytopenia and/or neutropenia and is defined as:

- Bone marrow blasts < 5%
- Absence of circulating blasts and blasts with Auer rods
- Absence of extramedullary disease
- Absolute neutrophil count > 0.5 x 10^9/L (500/μL)
- Platelet count > 50 x 10^9/L (50,000/μL)

Complete Response with Incomplete Blood Count Recovery (CRi)**

CRi requires all the CR criteria, except for residual neutropenia or thrombocytopenia and is defined as:

- Bone marrow blasts < 5%
- Absence of circulating blasts and blasts with Auer rod
- Absence of extramedullary disease
- Absolute neutrophil count ≤ 1.0 x 10^9/L (1000/μL) or platelet count ≤ 100 x 10^9/L (100,000/μL)

*Note: **If subjects meet criteria for both CRh and CRi, they should be classified as CRh*

Morphologic Leukemia Free State (MLFS)***

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

*Note: *** Marrow should not be merely "aplastic"; at least 200 cells should be enumerated or cellularity on bone marrow biopsy should be at least 10% of normal.*

Partial Response (PR)

PR meets all hematologic criteria of CR:

- Absolute neutrophil count > 1.0 x 10^9/L (1000/μL)

- Platelet count > 100 x 10^9/L (100,000/μL), and
- Residual bone marrow blast percentage of 5% to 25%
- Reduction of bone marrow blast percentage by ≥ 50% compared with pretreatment

Stable Disease (SD)

Absence of MRD negative CR, CR, CRh, CRi, PR, MLFS and criteria for PD not met.

Progressive Disease (PD)

Evidence for an increase in bone marrow blast percentage and/or circulating blast counts as defined by at least one of the following:

- > 50% increase in bone marrow blasts over baseline (a minimal absolute 15% increase is required in cases with < 30% blasts at baseline), or
- Persistent bone marrow blast percentage > 70% over ≥ 3 months without at least a 100% improvement in ANC to an absolute level > 0.5 x 10^9/L (500/μL) and/or platelet count to > 50 x 10^9/L (50,000/μL) without transfusion, or
- > 50% increase in circulating blasts to > 25 x 10^9/L (>25,000/μL) in the absence of Differentiation Syndrome,**** or
- New extramedullary disease

**** Certain targeted therapies, for example, those inhibiting mutant IDH proteins, other kinase or targets may cause a transient increase in the percentage of bone marrow blasts accompanied by an increase in circulating blasts (differentiation syndrome). In the setting of therapy with such compounds, an increase in blasts may not necessarily indicate progressive disease. Such instances should be discussed with the study medical monitor on a case-by-case basis.

Recurrence

Recurrence for subjects with prior MRD-CR, morphological CR, CRh, CRi, or MLFS is defined as:

Morphologic relapse as defined by the reappearance of circulating blasts or ≥ 5% blasts in the bone marrow not attributable to any other cause.

Note: In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5 to 20% blasts, a bone marrow aspirate/biopsy should be repeated within 1 week to distinguish relapse from bone marrow regeneration.

Reappearance of cytologically or biopsy documented extramedullary disease, including new CNS disease or other new sites of extramedullary involvement.

Note: The reappearance of a cytogenetic or molecular abnormality would be considered a cytogenetic or molecular relapse. In the absence of morphologic relapse, this would not be considered a recurrence.

10.5 Appendix 5: New York Heart Association Classification

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

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

10.6 Appendix 6: ECOG Performance Status Scale

Grade	ECOG
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, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Not confined to bed 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

Adapted from: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

10.7 Appendix 7: Potential for Drug-Drug Interactions

Concomitant administration of study treatment with medications listed below could result in drug-drug interactions that potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or ENTO.

The following list of prohibited medications is not comprehensive and only meant to be used as a guide.

Proton pump inhibitors*	Omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole, dexlansoprazole
Strong CYP3A inducers	Rifampin, mitotane, avasimibe, rifapentine, apalutamide, ivosidenib, phenytoin, carbamazepine, enzalutamide, St John's wort, lumacaftor, phenobarbital
Strong CYP2C9 inducers	(none reported)
Moderate CYP2C9 inducers	Rifampin, enzalutamide, ritonavir, carbamazepine

*Short term PPI use during the study treatment period (for up to 10 consecutive days) is permitted for management of acute gastrointestinal bleeding. Any requirement for longer exposures should prompt discontinuation of study medication per Section 7.1 (Need for or use of a prohibited concomitant medication).

A more comprehensive listing of strong CYP3A inducers, and strong or moderate CYP2C9 inducers to avoid can be found at: Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table, Indiana University School of Medicine (2007). https://drug-interactions.medicine.iu.edu

The following table lists dose adjustment requirements for concurrently administered HMG-CoA reductase inhibitors.

HMG-CoA Reductase Inhibitor	Dose Adjustment Required
Atorvastatin	Maximum dose 20 mg QD
Rosuvastatin	Maximum dose 10 mg QD
Pravastatin	Maximum dose 40 mg QD
Simvastatin	Maximum dose 20 mg QD
Lovastatin	Maximum dose 20 mg QD
Fluvastatin	Maximum dose 20 mg BID or 40 mg QD
Pitavastatin	Maximum dose 1 mg QD

10.8 Appendix 8: Recommended Adjustments to Anti-Platelet and Anti-Coagulant Therapy in AML

1. If aspirin is administered for primary prevention of cerebrovascular events, discontinue. If given for secondary prevention of cerebrovascular events, interrupt when platelets count is < 30,000/μL. Resume when platelet count is ≥ 30,000/μL.

2. Coronary artery stents (bare metal and drug eluting): Work closely with a consulting cardiologist to adjust anti-platelet therapy especially within first month of bare stent placement and first year of drug eluting stent placement. Consider holding aspirin and Plavix® when platelet count is < 20,000/μL and then resume when ≥ 20,000/μL if supported by cardiology consult recommendations, especially within first year of stent placement.

3. Atrial fibrillation: If patient is on aspirin only, hold when platelet count is < 50,000/μL and restart when consistently ≥ 50,000/μL. If patient is on anti-coagulant therapy (eg, Factor Xa antagonist), treat with therapeutic doses of low molecular weight heparin (LMWH) until platelet count is < 50,000/μL, treat with prophylactic doses for platelet counts between 20-50,000/μL and hold for platelet counts < 20,000/μL.

4. Mechanical heart valves: Work closely with a consulting cardiologist. Treat with therapeutic doses of LMWH until platelet count < 40,000/μL. Treat with prophylactic doses when platelet count is between 20-40,000/μL. Consider holding for platelet counts < 20,000/μL. Alternatively, consider platelet transfusions in order to allow continuation of anti-coagulant therapy, based on a recommendation from cardiology consultation.

5. Acute events:
    a. Catheter thrombosis: Remove catheter, consider anticoagulation if symptomatic and platelet count ≥ 50,000/μL.
    b. Distal thrombosis: Follow-up scans in 3 days and every week for 6 weeks to make sure thrombosis does not progress.
    c. Proximal thrombosis and pulmonary embolism: Treat with therapeutic doses of LMWH if platelet count is >40,000/μL, prophylactic doses if platelet count is 20-40,000/μL and retrievable inferior vena filter if platelet count is < 20,000/μL on a case-by-case basis after discussion with cardiology consult and the medical monitor.
6. Acute coronary syndrome: administer aspirin to all subjects, regardless of platelet count. Individualize therapy based on cardiology consultation (patient may need to discontinue study participation after discussion with medical monitor).

10.9 Appendix 9: Guidance on the Management of Clinical Trials During COVID-19 Pandemic

FDA Guidance on the Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency

EU Guidance on the Management of Clinical Trials During COVID-19 Pandemic

Supplementary Recommendations to EU Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic

Contains Nonbinding Recommendations

Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency

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Guidance for Industry, Investigators, and Institutional Review Boards

March 2020

Updated on August 30, 2021

For questions on clinical trial conduct during the COVID-19 pandemic, please email [redacted]

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Office of Good Clinical Practice (OGCP)

Contains Nonbinding Recommendations

Preface

Public Comment

This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number FDA-2020-D-1106 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA web page titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," *available at* https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders, and the FDA web page titled "Search for FDA Guidance Documents," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. You may also send an email request to [redacted] to receive an additional copy of the guidance. Please include the docket number FDA-2020-D-1106 and complete title of the guidance in the request.

Questions

For questions about this document, contact us via email at [redacted]

Contains Nonbinding Recommendations

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Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency

Guidance for Industry, Investigators, and Institutional Review Boards

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. Introduction

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to provide general considerations to assist sponsors in assuring the safety of trial participants,[1] maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity for the duration of the COVID-19 public health emergency. This document updates the guidance of the same title issued in January 2021 (previous versions December, September, July, June, May, April, and March 2020). The appendix to this guidance further explains those general considerations by providing answers to questions that the Agency has received about conducting clinical trials during the COVID-19 public health emergency.

[1] In this document, the terms *trial participant* or *participant* are used and are interchangeable with the term *subject* as used in referenced FDA regulations.

This policy is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services (HHS) on January 31, 2020, effective January 27, 2020, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (PHS Act) (42 U.S.C. 247d(a)(2)).

Given this public health emergency, and as discussed in the Notice in the *Federal Register* of March 25, 2020 (85 FR 16949), titled "Process for Making Available Guidance Documents Related to Coronavirus Disease 2019," available at https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

II. Background

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.[2] In addition, on March 13, 2020, there was a Presidential declaration of a national emergency in response to COVID-19.[3]

FDA recognizes that the COVID-19 public health emergency may impact the conduct of clinical trials of medical products. Challenges may arise, for example, from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product,[4] or other considerations if site personnel or trial participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including

[2] Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), available at https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.

[3] Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (Mar. 13, 2020), available at https://trumpwhitehouse.archives.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/.

[4] For the purposes of this guidance, the term *investigational product* refers to human drugs and biological products, as well as medical devices.

administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing. FDA recognizes that protocol modifications may be required, and that there may be unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 public health control measures. Although the necessity for, and impact of, COVID-19 public health control measures on trials will vary depending on many factors, including the nature of disease under study, the trial design, and in what region(s) the study is being conducted, FDA outlines the following general considerations to assist sponsors in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity. The appendix further explains those general considerations by providing answers to questions about conducting clinical trials that the Agency has received during the COVID-19 public health emergency.

III. Discussion

A. Considerations for ongoing trials:

- Ensuring the safety of trial participants is paramount. Sponsors should consider each circumstance, focusing on the potential impact on the safety of trial participants, and modify study conduct accordingly. Study decisions may include those regarding continuing trial recruitment, continuing use of the investigational product for patients already participating in the trial, and the need to change patient monitoring during the trial. In all cases, it is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them.

- Sponsors, in consultation with clinical investigators and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), may determine that the protection of a participant's safety, welfare, and rights is best served by continuing a study participant in the trial as per the protocol or by discontinuing the administration or use of the investigational product or even participation in the trial. Such decisions will depend on specific circumstances, including the nature of the investigational product, the ability to conduct appropriate safety monitoring, the potential impact on the investigational product supply chain, and the nature of the disease under study in the trial.

- Since trial participants may not be able to come to the investigational site for protocol-specified visits, sponsors should evaluate whether alternative methods for safety assessments (e.g., phone contact, virtual visit, alternative location for assessment, including local labs or imaging centers) could be implemented when necessary and feasible, and would be sufficient to assure the safety of trial participants. Sponsors should determine if in-person visits are necessary to fully assure the safety of trial participants (for example, to carry out procedures necessary to assess safety or the safe use of the investigational product appropriately); in making the decision to continue use or administration of the investigational product, the sponsor should consider whether the safety of trial

participants can be assured with the implementation of the altered monitoring approach.

- In some cases, trial participants who no longer have access to investigational product or the investigational site may need additional safety monitoring (e.g., on withdrawal of an active investigational treatment).

- The need to put new processes in place or to modify existing processes will vary by the protocol and local situation. For example, this assessment could include consideration of whether it is appropriate to delay some assessments for ongoing trials, or, if the study cannot be properly conducted under the existing protocol, whether to stop ongoing recruitment, or even withdraw trial participants.

- COVID-19 screening procedures that may be mandated by the health care system in which a clinical trial is being conducted do not need to be reported as an amendment to the protocol, even if done during clinical study visits, unless the sponsor is incorporating the data collected as part of a new research objective.

- Changes in a protocol are typically not implemented before review and approval by the IRB/IEC, and in some cases, by FDA. Sponsors and clinical investigators are encouraged to engage with IRBs/IEC as early as possible when urgent or emergent changes to the protocol or informed consent are anticipated as a result of COVID-19. Such changes to the protocol or investigational plan to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19) may be implemented without IRB approval or before filing an amendment to the investigational new drug (IND) or investigational device exemption (IDE), but are required to be reported afterwards.[5] FDA encourages sponsors and investigators to work with their IRBs to prospectively define procedures to prioritize reporting of deviations that may impact the safety of trial participants.

- The implementation of alternative processes should be consistent with the protocol to the extent possible, and sponsors and clinical investigators should document the reason for any contingency measures implemented. Sponsors and clinical investigators should document how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes, indicate which trial participants were impacted, and how those trial participants were impacted.

- Changes in study visit schedules, missed visits, or patient discontinuations may lead to missing information (e.g., for protocol-specified procedures). It will be important to capture *specific* information in the case report form that explains the basis of the missing data, including the relationship to COVID-19, for missing protocol-specified information (e.g., from missed study visits or study

[5] See 21 CFR 56.108(a)(4), 56.104(c), 312.30(b)(2)(ii), and 812.35(a)(2).

discontinuations due to COVID-19). This information, summarized in the clinical study report, will be helpful to the sponsor and FDA.

- If scheduled visits at clinical sites will be significantly impacted, certain investigational products, such as those that are typically distributed for self-administration, may be amenable to alternative secure delivery methods. For other investigational products that are normally administered in a health care setting, consulting FDA review divisions on plans for alternative administration (e.g., home nursing or alternative sites by trained but non-study personnel) is recommended. In all cases, existing regulatory requirements for maintaining investigational product accountability remain and should be addressed and documented.

- With respect to efficacy assessments, FDA recommends consultation with the appropriate review division regarding protocol modifications for the collection of efficacy endpoints, such as use of virtual assessments, delays in assessments, and alternative collection of research-specific specimens, if feasible. For individual instances where efficacy endpoints are not collected, the reasons for failing to obtain the efficacy assessment should be documented (e.g., identifying the specific limitation imposed by COVID-19 leading to the inability to perform the protocol-specified assessment).

- If changes in the protocol will lead to amending data management and/or statistical analysis plans, the sponsor should consider doing so in consultation with the applicable FDA review division. Prior to locking the database, sponsors should address in the statistical analysis plan how protocol deviations related to COVID-19 will be handled for the prespecified analyses.

- If planned on-site monitoring visits are no longer possible, sponsors should consider optimizing use of central and remote monitoring programs to maintain oversight of clinical sites.

B. In general, and if policies and procedures <u>are not already in place</u> for applicable trials:

- Sponsors, clinical investigators, and IRBs should consider establishing and implementing policy and procedures, or revise existing policy and procedures, to describe approaches to be used to protect trial participants and manage study conduct during possible disruption of the study as a result of COVID-19 control measures at study sites. Changes to policy and procedures could address, but not be limited to, impact on the informed consent process, study visits and procedures, data collection, study monitoring, adverse event reporting, and changes in investigator(s), site staff, and/or monitor(s) secondary to travel restrictions, quarantine measures, or COVID-19 illness itself. Policy and procedures should be compliant with applicable (regional or national) policy for the management and control of COVID-19. Depending upon the nature of the

changes described above, a protocol amendment may be required under the applicable regulations.[6]

C. For all trials that are impacted by the COVID-19 public health emergency:

Sponsors should describe in appropriate sections of the clinical study report (or in a separate study-specific document):

1. Contingency measures implemented to manage study conduct during disruption of the study as a result of COVID-19 control measures.

2. A listing of all participants affected by the COVID-19 related study disruption by unique trial participant number identifier and by investigational site, and a description of how the individual's participation was altered.

3. Analyses and corresponding discussions that address the impact of implemented contingency measures (e.g., trial participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study.

Robust efforts by sponsors, investigators, and IRBs/IECs to maintain the safety of trial participants and study data integrity are expected, and such efforts should be documented. As stated above, FDA recognizes that protocol modifications may be required, including unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 control measures. Efforts to minimize impacts on trial integrity, and to document the reasons for protocol deviations, will be important.

IV. Additional Resources

For further questions on clinical trial conduct during the COVID-19 public health emergency, please email [redacted]

Contact information for FDA's review divisions is as follows:

CDER: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-new-drugs.

CBER: https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/contacts-center-biologics-evaluation-research-cber#indcont.

CDRH: https://www.fda.gov/about-fda/cdrh-offices/cdrh-management-directory-organization.

[6] See 21 CFR 312.30(b) and 812.35(a). Under applicable Federal regulations, investigators must engage with the Drug Enforcement Administration when amending protocols for research involving Schedule I substances under the Controlled Substances Act by requesting a modification to a site-specific investigator registration (see 21 CFR 1301.18).

Appendix: Questions and Answers

Q1. What are some of the key factors that a sponsor should consider when deciding whether to suspend or continue an ongoing study or to initiate a new study during the COVID-19 public health emergency?

Central to any decision should be ensuring that the safety of clinical trial participants can be maintained. Sponsors, in consultation with clinical investigators and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), should assess whether the protection of a participant's safety, welfare, and rights is best served by continuing a study participant in the trial as per the protocol or by discontinuing the administration or use of the investigational product or even participation in the trial. Such decisions will depend on specific circumstances, including the nature of the investigational product, the ability to conduct appropriate safety monitoring, the potential impact on the investigational product supply chain, and the nature of the disease under study in the trial. As part of this assessment, sponsors should carefully consider the following aspects of clinical trial conduct when deciding how or whether to proceed with a clinical trial:

- Assessing whether the limitations imposed by the COVID-19 public health emergency on protocol implementation pose new safety risks to trial participants, and whether it is feasible to mitigate these risks by amending study processes and/or procedures.

- Assessing the continued availability of the clinical investigator/sub-investigators to provide oversight of the trial and properly assess and manage safety issues that may emerge.

- Assessing whether there will be sufficient clinical trial support staff given the evolving COVID-19 situation and its impact on staff availability. Are there appropriately trained staff that could be available to handle the expected tasks? Is there adequate equipment and materials for clinical trial support staff?

- Assessing whether clinical investigator sites will remain open to trial participants for required in-person assessments or whether the clinical investigator has the ability to provide required in-person assessments at an acceptable alternate location(s), or whether such protocol-specified, in-person assessments can instead be conducted virtually.

- Assessing the continued availability of clinical trial supplies and continued operations of vendors, especially related to supply of the investigational product and/or to clinical trial supplies that are essential to maintaining appropriate safety monitoring or other key trial procedures. This should include consideration of product stability (shelf life) if the treatment schedule is revised, or if the clinical site is unable to properly store the product for the needed duration.

- Assessing the continued availability of, and support for, information technology systems and any other technological tools that are needed to support the trial. Are current contingency plans adequate for the types of disruptions that might be

anticipated? What other plans can be put in place to minimize any potential disruptions?

- Assessing whether there will be continued operations of, and adequate communications with, IRB/IEC and Data Monitoring Committee (DMC) staff, if applicable, to support trial needs.

- Assessing whether it is feasible to conduct the trial in light of any COVID-19 public health measures implemented by Federal and State authorities to control the virus.

Involvement of a study's DMC, if one has been established, can provide support for the assessments discussed above. Since a primary responsibility of the DMC is assuring the safety of participating trial participants, the DMC's assessment of the impact of modifications of trial conduct due to COVID-19 on patient safety is important to consider.

The risks and benefits of continuing a trial are likely different than a decision to initiate a trial (other than trials intended to evaluate investigational treatments or vaccines for COVID-19). Given the evolving situation, with likely increasing impacts on investigators, staff, and supply chains, sponsors should carefully consider the ability to effectively mitigate risks such that patient safety and trial integrity are assured. In addition, it is important to consider whether initiation of the trial could interfere with public health measures implemented by Federal and State authorities to control the virus.

Q2. What key factors should sponsors consider when deciding whether to continue administering or using an investigational product that appears to be providing benefit to the trial participant during the COVID-19 public health emergency?

There may be circumstances in which an investigational product (either a drug, biological product, or medical device) appears to be providing benefit to the trial participant. A sponsor deciding whether to continue administering or using such a product during the COVID-19 public health emergency should carefully consider context-dependent issues, including whether a trial participant appears to be benefitting from treatment with the investigational product, whether there are reasonable alternative treatments, the seriousness of the disease or condition being treated, and the risks involved in switching to an alternative treatment if necessary. FDA recognizes that in some circumstances it may be necessary (e.g., based on lack of product supply or inability to administer or ensure the safe use of the investigational product) to discontinue investigational product administration in a trial. If there are individual trial participants for whom discontinuing the investigational product might present a substantial risk (e.g., trial participants perceived by the investigator as having a clinical benefit from the investigational product), the sponsor should consider amending the protocol, after discussion with the relevant review division, to limit investigational product use to those patients with apparent benefit and discontinue investigational product use to other participants. In all cases, if a trial participant is discontinued from an investigational therapy, it is important that there be appropriate management after discontinuation.

Q3. How should sponsors manage protocol deviations and amendments to ongoing trials during the COVID-19 public health emergency?

FDA recognizes that during the COVID-19 public health emergency, sponsors of clinical trials may need to modify protocol-specified procedures. As is discussed in the main body of this guidance, for protocol deviations necessitated by the impact of the current COVID-19 public health emergency, the sponsor should document the specific protocol deviation and the reason for the deviation. The sponsor can document protocol deviations using its standard processes, or given the larger expected number of such deviations, use alternative documentation approaches. For example, if visits are to be conducted by telephone/video contact rather than at the investigational site as specified in the protocol, documentation that provides a listing of all study visits (e.g., listing study reference number, patient ID, date of visit) that are deviations from the protocol due to the current COVID-19 situation generally would be acceptable. Protocol deviations should be included in final study reports and may also be included in annual reports.

For a study-wide change in protocol conduct, under the IND regulations protocol amendments that are necessary to prevent imminent hazards to trial participants can generally be immediately implemented with subsequent submission and formal approval by the IRB and notification to FDA through filing a protocol amendment to the IND.[7]

For studies under an IND, 21 CFR 312.30(b) specifies that sponsors must submit a protocol amendment to the IND describing any change in a phase 1 protocol that significantly affects the safety of trial participants or any change in a phase 2 and 3 protocol that significantly affects the safety of trial participants, the scope of the investigation, or the scientific quality of the study. Pausing enrollment in a trial to decrease potential exposure to COVID-19 would not generally be expected to significantly affect trial participant safety, the scope of the investigation, or the scientific quality of the study; therefore, submitting a protocol amendment would not be required under the regulation for such a pause.

Protocol amendments that are not required to prevent imminent safety risks to patients can be implemented after they are submitted to FDA and IRB approval has occurred.[8]

FDA recognizes that during the rapidly evolving circumstances of the current COVID-19 public health emergency, a sequence of changes may be needed to address those circumstances. Clinical investigators must document as protocol deviations any modifications to protocol-specified procedures that occur prior to IRB approval and submission of the protocol amendment implementing the modification.[9] Consolidating several protocol modifications in a single protocol amendment would be acceptable but should be submitted expeditiously.

For studies under an IDE, 21 CFR 812.35(a) generally requires prior FDA approval before implementing changes to the investigational plan. These requirements do not apply to changes made to protect the life or physical well-being of a trial participant in an emergency, including

[7] See 21 CFR 56.108(a)(4) and 312.30(b)(2)(ii).
[8] See 21 CFR 312.30(b)(2).
[9] See 21 CFR 312.62.

study-wide changes, but such deviations must be reported to FDA within 5 working days.[10] In addition, under 21 CFR 812.35(a)(3), changes to the protocol that the sponsor determines, based on credible information, do not affect the validity of the results from the study, the likely patient risk-to-benefit relationship, the scientific soundness of the investigational plan, or the rights, safety, or welfare of the trial participants may be made without prior FDA approval, if the sponsor reports the modifications to the agency within 5 days of implementing the changes. Because of the unique and evolving circumstances surrounding the impact of COVID-19, we understand that it may be challenging to submit 5-day reports/notices within the required timeframe. Sponsors may consolidate implemented changes when submitting 5-day reports/notices and should update the IDE as soon as possible.

Q4. How should a sponsor submit a change in protocol that results from challenges related to the COVID-19 public health emergency?

For **IND studies**, the sponsor should submit a formal amendment to its IND, with the following information added to the cover letter in the subject line:

PROTOCOL AMENDMENT – COVID-19

TITLE OF PROTOCOL

Sponsors should summarize the major changes made to the protocol related to COVID-19 in the cover letter and should include a tracked changes version of the protocol to facilitate review. As with other protocol amendments, sponsors may implement protocol amendments due to COVID-19 upon submission to FDA if approved by the IRB. Sponsors seeking FDA input prior to implementation should indicate that in the cover letter.

For IDE studies, the sponsor should submit a supplement to its existing IDE, with the following information added to the cover letter in the subject line:

CHANGE IN PROTOCOL SUPPLEMENT – COVID-19 or
NOTICE OF IDE CHANGE – COVID-19, as applicable

TITLE OF PROTOCOL

The submission to the IDE should contain a tracked changes version of the protocol to facilitate review.

Q5. Can a sponsor initiate virtual clinical trial visits for monitoring patients without contacting FDA if there is an assessment by the sponsor and investigator that these visits are necessary for the safety of the trial participant and it will not impact data integrity?

FDA regulations allow for changes to be made to the investigational plan or protocol without prior FDA review or approval, if the change is intended to eliminate an apparent immediate

[10] See 21 CFR 812.35(a)(2).

hazard or to protect the life and well-being of trial participants.[11] Therefore, changes in protocol conduct necessary to immediately assure patient safety, such as conducting telephone or video contact visits for safety monitoring rather than on-site visits, can be immediately implemented with subsequent review by the IRB and notification to FDA. Since this reflects a protocol deviation (until the amendment is approved), documentation of the required deviations, as described above, would generally be acceptable (i.e., a document that lists each deviation, study reference ID, patient ID, and date). For example, documenting that all protocol-specified visits will be done by telephone contact rather than on-site visits, and that procedures requiring in-person visits will either not be conducted, or performed by other means (specified, as appropriate). Since the change to telephone or video contact visits would likely result in some protocol-required procedures not being conducted (e.g., vital signs, blood samples for safety laboratory studies), the sponsor must evaluate the potential impact on patient safety, and consider how to mitigate risks to patients, including the need to discontinue the investigational product.

For IDE studies, sponsors are required to report deviations implemented to address the imminent safety risk to FDA within 5 working days after learning of the deviations. We recognize that challenges related to the COVID-19 pandemic may make it difficult to meet this timeframe. Sponsors may consolidate implemented deviations when submitting 5-day reports and should update FDA as soon as possible.

Q6. With the rapid changes in clinical trial conduct that may occur due to the COVID-19 public health emergency, including multiple deviations to address patient safety, what is the best way for sponsors and investigators to capture these data?

As noted in the main body of this guidance, it is important to capture *specific* information for individual participants that explains the basis for missing protocol-specified information that includes the relationship to COVID-19 (e.g., from missed study visits or study discontinuations due to COVID-19). This information, summarized in the clinical study report, will be helpful to the sponsor and FDA. If it is not possible to capture this information in the case report form(s), sponsors may develop processes that enable systematic capture of these data across the sites in a manner that enables the appropriate analysis when the data are submitted to FDA. Sponsors may also develop processes to capture site-level status, site-level or vendor-level protocol deviations, and process deviations.

Q7. If patients are currently dispensed investigational product through a pharmacy at the clinical trial site for self-administration at home, can a sponsor switch that to home delivery without amending the protocol?

If there is concern about risk of exposure to COVID-19, home delivery of investigational product that would not raise any new safety risks may be implemented to protect patients from coming to clinical trial sites. In all cases, requirements under FDA regulations for maintaining required investigational product storage conditions and investigational product accountability remain; these requirements must be addressed and documented.[12] If the protocol indicates pharmacy dispensing for self-administration at home, and this is changed to direct-to-patient shipments,

[11] See 21 CFR 56.108(a)(4), 312.30(b)(2)(ii), and 812.35(a)(2).
[12] See 21 CFR 312.60, 312.62, and 812.140.

then a protocol amendment would be required to permit home delivery of investigational product.[13] If the extent of home delivery is limited to certain participants and not the entire population described in the protocol, documenting the change in the mechanisms of distribution of investigational product administration through protocol deviations may also be acceptable. If the change in the mechanisms of investigational product distribution is then included in a protocol amendment, such a change may be part of a "cumulative" amendment that includes a number of changes that accrue, rather than an urgent protocol change.[14]

Q8. How can the sponsor ensure proper disposal of unused investigational drug product if the participant cannot return to the study site?

FDA regulations outline sponsor and investigator responsibilities for storage conditions and accountability of investigational drug products, including disposition of unused investigational products (IPs).[15] Under 21 CFR 312.59, the sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator. The regulation further provides that the sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative does not expose humans to risks from the drug. The procedure for disposition is generally considered part of the investigational plan and is normally described in the study protocol as a study-specific plan for handling the IPs. In most protocols, such plans involve the participant bringing the unused IP to the clinical trial site and then the investigator returning the unused IP to the sponsor or its designee. During the COVID-19 public health emergency, if appropriate, a pre-paid shipping package can be used for the participant to return IP back to a central location where it can be accounted for and disposed of per the protocol, but this approach is not the only way to satisfy the regulatory requirements for disposition of unused IP. Regardless of the chosen disposition method, sponsors and investigators must maintain adequate records regarding the disposition of the IP.[16]

Sponsors may consider adopting alternative procedures for disposition of IP that permit sponsors and investigators to fulfill their requirements for maintaining adequate records of IP disposition (including documenting dates, quantity, and use by particpants), provided such procedures do not expose humans to risks from the IP.[17] For example, it may be possible to provide the participants with a way to dispose of IP at their home (such as with a drug disposal pouch) and document such disposal through photo or video that can be transmitted to the investigator or sponsor. FDA does not endorse a particular approach, but the risks involved (e.g., environmental considerations) with specific IPs should be considered when selecting a method for disposal. FDA has provided a consumer update *Where and How to Dispose of Unused Medicines*[18] that provides recommendations to consumers about how to safely dispose of unused FDA-approved medication at home. Sponsors can consider whether any of those recommended methods of disposition are appropriate for approved drugs being studied for a new use in a clinical

[13] See 21 CFR 312.30(b) and 812.35(a).
[14] See 21 CFR 312.30(b), 812.35(a), and 812.150(a)(4).
[15] See 21 CFR 312.57, 312.59, 312.60, and 312.62.
[16] See 21 CFR 312.57 and 312.62.
[17] Sponsors should consider whether an information amendment should be submitted pursuant to 21 CFR 312.31.
[18] See https://www.fda.gov/consumers/consumer-updates/where-and-how-dispose-unused-medicines.

investigation. As noted in the consumer update, FDA only recommends flushing medications that are on the FDA flush list, which currently does not include unapproved IP.

Investigators proposing alternative disposition methods must obtain authorization of those methods from the sponsor of the trial.[19] Additional restrictions may apply to IPs subject to the Controlled Substances Act.[20]

Q9. If patients are currently receiving an investigational product infusion at the clinical trial site, can a sponsor switch to home infusion?

Sponsors should consider the safety risk to trial participants who would miss an investigational product infusion because of the inability to come to the clinical trial site. If a sponsor is considering providing alternative arrangements for administration of the investigational product (e.g., home nursing or alternative sites by trained but non-study personnel), the sponsor is expected to perform a risk assessment that considers the nature of the investigational product and the potential risks to both the trial participants and the health care providers responsible for administering the product at the alternative site. This risk assessment should include assessment of risk mitigation strategies. Based on this risk assessment, sponsors should consider whether consulting the appropriate FDA review divisions regarding plans for alternative arrangements for administration of investigational products that are usually administered in a health care setting is warranted.

Consulting FDA is strongly advised for complex investigational products (e.g., cellular therapy and gene therapy products), where potentially altered storage and handling conditions could adversely affect product stability. In all cases, applicable requirements for maintaining required investigational product storage conditions (prior and after reconstitution), investigational product reconstitution specifications per the Investigator's Brochure, and investigational product accountability remain and must be addressed and documented. Storage conditions and investigational product accountability should be considered if the protocol is amended to permit alternative site infusions. Defining circumstances when discontinuing investigational product administration, while continuing study participation, albeit with potentially delayed assessments, may be an appropriate option when suitable alternative arrangements cannot be made.

Q10. Considering that there likely will be delays to on-site monitoring of clinical trials during the COVID-19 public health emergency, what are FDA's expectations in such circumstances?

FDA recognizes that monitors may not be able to access the trial sites for on-site visits in a timely manner during the COVID-19 public health emergency. Sponsors should work to find alternative approaches to maintain trial participant safety and trial data quality and integrity, such as enhanced central monitoring, telephone contact with the sites to review study procedures, trial participant status and study progress, or remote monitoring of individual enrolled trial participants, where appropriate and feasible. FDA recognizes that delays in on-site monitoring may result in delayed identification of GCP non-compliance (including major protocol

[19] See 21 CFR 312.59 and 21 CFR 312.62.
[20] See 21 CFR 312.58(b) and 312.69

deviations) at the clinical trial site(s) (including protocol deviations not due to the impact of COVID-19). Sponsors should carefully document situations where monitors were unable to access, or had to delay monitoring of, a clinical site. Sponsors/monitors should also include in their documentation of protocol deviations or other GCP non-compliance issues identified at clinical sites whether delayed identification was due to postponed monitoring. FDA recognizes that unique situations at clinical sites will occur due to COVID-19 control measures and will consider these circumstances when evaluating inspectional observations.

Q11. How do I obtain signed informed consent from a hospitalized patient who is in isolation when a COVID-19 infection control policy prevents us from entering the patient's room to collect a signed informed consent form?

FDA regulations generally require that the informed consent of a trial participant (in this case, a hospitalized patient) be documented by the use of a written consent document that typically includes the elements of informed consent, as described in 21 CFR 50.25, and that has been approved by the IRB and signed and dated by the trial participant or their legally authorized representative at the time of consent (21 CFR 50.27(a)). When feasible, we recommend a traditional method of obtaining and documenting informed consent using a signed paper copy of the consent form, or use of electronic informed consent.[21, 22, 23] If neither of these approaches are possible, the following procedures would be considered to satisfy FDA's informed consent documentation requirement.[24]

Method 1: A photograph of the signed informed consent document can be transmitted to the trial staff

1. An unsigned consent form is provided to the patient by a person who has entered the room.

2. The investigator/designee arranges a telephone call or video conference call with the patient (and, if desired and feasible, additional individuals requested by the patient (e.g., next of kin)).

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[21] See the guidance for institutional review boards, investigators, and sponsors *Use of Electronic Informed Consent in Clinical Investigations* (December 2016). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www fda.gov/regulatory-information/search-fdaguidance-documents.

[22] For example, for FDA-regulated trials conducted during the COVID-19 public health emergency, FDA has made the COVID MyStudies app available in the Apple App and Google Play stores as a platform enabling investigators to obtain informed consent securely from patients when face-to-face contact is not possible or practical due to COVID-19 public health measures to control the virus. To facilitate free use of the app during the public health emergency, FDA intends to fund the technical assistance required to operate the COVID MyStudies app, which will be provided by the Harvard Pilgrim Healthcare Institute, as resources permit. For more information, investigators interested in using the app should see https://www.fda.gov/drugs/science-and-research-drugs/covid-mystudies-application-app.

[23] See Q25.

[24] The procedures suggested do not apply to the exception from general informed consent requirements under 21 CFR 50.23 or the exception from informed consent requirements for emergency research under 21 CFR 50.24.

3. To ensure that patients are approached in a consistent fashion, a standard process should be used that will accomplish the following:

    - Identification of who is on the call.

    - Review of the informed consent document with the patient by the investigator/designee and response to any questions the patient may have.

    - Verbal confirmation by the patient that their questions have been answered, that they would like to participate in the trial, and that they have signed and dated the informed consent document that is in their possession.

4. The patient (or an individual in the room) takes a photograph of the signed informed consent document and sends it to the investigator/designee.

5. A trial team member enters the photograph into the trial records along with an attestation that states how that photograph was obtained and that it is a photograph of the informed consent document signed by the patient.

Method 2: A witness can attest to the signature, but a photograph of the signed informed consent document cannot be transmitted

1. An unsigned consent form is provided to the patient by a person who has entered the room.

2. The investigator/designee arranges a three-way telephone call or video conference call with the patient, a witness who is not otherwise connected with the clinical investigation, and, if desired and feasible, additional individuals requested by the patient (e.g., next of kin). Alternatively, in lieu of using a witness, a recording of the conversation can be made.[25]

3. To ensure that patients are approached in a consistent fashion, a standard process should be used that will accomplish the following:

    - Identification of who is on the call.

    - Review of the informed consent document with the patient by the investigator/designee and response to any questions the patient may have.

    - Verbal confirmation by the patient that their questions have been answered, that they would like to participate in the trial, and that they have signed and dated the informed consent document that is in their possession.

[25] If an investigator wants to record the telephone or video conference call, the investigator/designee should ensure that the recording is done in a manner consistent with applicable State and local laws and that all parties agree to being recorded.

4. When using a witness, documentation in the trial records includes: (1) a signed and dated attestation by the witness who participated on the call that the patient confirmed their agreement to participate in the trial and signed the informed consent document; and (2) a signed and dated attestation by the investigator/designee stating why the informed consent document signed by the patient was not retained (e.g., due to potential contamination of the document by infectious material).

   When using a recording in lieu of a witness, documentation in the trial records includes: (1) the recording of the conference call; and (2) a signed and dated attestation by the investigator/designee who participated on the call stating why the informed consent document signed by the patient was not retained (e.g., due to potential contamination of the document by infectious material).

When either Method 1 or 2 is used to document informed consent, the resulting documentation should be: (1) collected and archived, as either original paper copies or appropriately certified electronic copies (e.g., using a validated process for scanning paper copies),[26] and (2) retained according to applicable FDA record retention requirements as part of the trial record.[27]

If the patient is unable to provide informed consent and there is a legally authorized representative, investigators must obtain written consent from the patient's legally authorized representative in accordance with 21 CFR 50.27(a).

Q12. How do I obtain informed consent from a patient unable to travel to a clinical trial site where electronic informed consent is not an option?

Investigators may also need to obtain informed consent from a potential trial participant or their legally authorized representative when these individuals are unable to travel to the site where the investigator is located due to COVID-19 illness or travel restrictions. When investigators do not have electronic informed consent (eIC) capabilities,[28] methods of obtaining informed consent other than a face-to-face consent interview may still be acceptable if those methods allow for an adequate exchange of information and documentation, and a method to ensure that the signer of the consent form is the person who plans to enroll as a participant in the clinical investigation or is the legally authorized representative of the trial participant. For example, the consent form may be sent to the trial participant or their legally authorized representative by facsimile or email, and the consent interview may then be conducted by telephone when the trial participant or their legally authorized representative can read the consent form during the discussion. After the consent discussion, the trial participant or their legally authorized representative can sign and date the consent form.

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[26] FDA guidance on good clinical practice developed with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) defines a certified copy as "[a] copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original." See the ICH guidance for industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018), available on the FDA guidance web page.

[27] See 21 CFR 312.57, 312.62, and 812.140.

[28] See footnote 19.

Options for returning the document to the clinical investigator may include facsimile, a photographic image sent through electronic means, scanning the consent form and returning it through a secure email account, or posting it to a secure Internet address, especially if there are concerns about having the participant mail a potentially contaminated consent document. Alternatively, the trial participant may bring the signed and dated consent form to his/her next visit to the clinical site, if restrictions on traveling to the clinical trial site are alleviated or mail it to the clinical investigator. The case history for each trial participant must document that informed consent was obtained prior to participation in the trial.[29] In addition, the person signing the consent form must receive a copy of the consent form.[30] Although FDA regulations do not require the trial participant's copy to be a signed copy, FDA recommends that a copy of the signed consent form be provided.

The trial participant or their legally authorized representative must sign and date the informed consent form before the investigator may conduct any study-related procedures involving the participant.[31] Where it is not feasible for investigators to receive the signed consent form prior to beginning study-related procedures, the investigators should have the prospective trial participant or legally authorized representative confirm verbally during the consent interview that the participant or legally authorized representative has signed and dated the form. In addition, the overseeing IRB must review and approve the planned informed consent process.[32]

Q13. How can informed consent be obtained and documented from a prospective trial participant (or legally authorized representative) when they cannot print and sign a paper copy of the consent form provided electronically by the investigator/designee, they cannot electronically sign the informed consent form, and providing a paper copy of the consent form via mail/courier is not feasible within the time frame for enrollment into the clinical trial?

Where a prospective trial participant (or legally authorized representative) is unable to print the informed consent document provided electronically by the investigator/designee, an electronic signature process is not available, and the prospective trial participant must meet time-sensitive eligibility criteria, the investigator may consider using the following alternative process to satisfy FDA requirements for obtaining and documenting informed consent:

1. The investigator/designee provides the prospective participant (or legally authorized representative) with an electronic version of the informed consent document.

2. The investigator/designee arranges a telephone call or video conference call with the prospective participant (or legally authorized representative), the investigator/designee, a witness who is not otherwise connected with the clinical investigation and, if desired and feasible, additional participants requested by the

[29] See 21 CFR 312.62(b) and 812.140(a)(3)
[30] See 21 CFR 50.27(a).
[31] See 21 CFR 50.20 and 50.27(a).
[32] See 21 CFR 50.27(a), 56.103(a), and 56.111(a).

prospective participant (e.g., next of kin). Alternatively, in lieu of using a witness, a recording of the conversation can be made.[33]

3. To ensure that the prospective participant (or legally authorized representative) is approached in a consistent fashion, a standard process should be used that will accomplish the following:

    a. Identification of who is on the call.

    b. Review of the informed consent document with the prospective participant (or legally authorized representative) by the investigator/designee and response to any questions the prospective participant (or legally authorized representative) may have.

    c. Verbal confirmation by the prospective participant (or legally authorized representative) that their questions have been answered and that they would like to participate in the trial.

4. Verbal confirmation by the participant (or legally authorized representative) that they signed and dated a blank piece of paper with a written statement that they voluntarily agree to participate in the protocol, noting both the Protocol 'NUMBER' and brief protocol title.

5. After signing and dating the newly created document, the trial participant (or legally authorized representative) sends a photograph of the signed and dated statement by facsimile, text message, or email to the investigator/designee; OR returns the document to the investigator by mail at a later date, or at a future study visit that might occur in person.

6. When using a witness, documentation in the trial records includes a signed and dated attestation by the witness who participated on the call that the patient confirmed their agreement to participate in the trial and signed the document referenced above.

7. When using a recording in lieu of using a witness, documentation in the trial records includes the recording of the conference call.

8. After the signed and dated document is received by trial staff, it should be appended to a copy of the consent document that was reviewed with the trial participant (or their legally authorized representative) and retained in the trial records as would normally be done for a signed informed consent document. Additionally, a note in the trial records should be made explaining the circumstances of why informed consent was obtained through an alternative

[33] If an investigator wants to record the telephone or video conference call, the investigator/designee should ensure that the recording is done in a manner consistent with applicable State and local laws and that all parties agree to being recorded.

method. The case history for each trial participant must document that informed consent was obtained prior to participation in the trial.[34]

This alternative approach must be reviewed and approved by the IRB overseeing the trial as required under FDA regulations.[35]

Q14. What factors should sponsors consider when deciding whether to change their clinical trial protocol during the COVID-19 public health emergency to include remote clinical outcome assessments?

Some clinical outcome assessments (COAs)[36] can be conducted remotely in clinical trials during the COVID-19 public health emergency, including COAs for performance outcome (PerfO), interview-based clinician-reported outcome (ClinRO),[37] patient-reported outcome (PRO), and observer-reported outcome (ObsRO). During the COVID-19 public health emergency, sponsors may still be conducting in-person assessments on some trial participants, whereas remote assessments may be necessary for others to protect their safety or to respond to COVID-19-related public health measures implemented by government authorities to control the virus. When deciding whether to change their clinical trial protocols to include remote COAs, sponsors should evaluate the general and specific considerations outlined below.

General considerations regarding (1) prioritization of trial participant safety and privacy; (2) maintenance of data quality and integrity, including minimizing missing data; and (3) appropriate training for personnel and trial participants, which are discussed elsewhere in this guidance, are also common to all COAs. Other general considerations that are common to all COAs include attention to (1) the potential for increased variability in trial data; (2) the feasibility of conducting a specific type of COA remotely, depending on the context of use; (3) documentation and audit trails; and (4) availability of technology and technical support required for remote assessment. These considerations are explained in more detail below.

Increased Variability in Data: When switching from in-person to remote assessments, sponsors should perform remote assessments in a manner as similar as possible to those done in-person, while protecting trial participant safety and privacy. To the extent feasible, sponsors

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[34] See 21 CFR 312.62(b) and 812.140(a)(3)

[35] See 21 CFR 50.27, 56.103, and 56.108(a).

[36] For purposes of this guidance, a *COA* is an assessment of a clinical outcome (i.e., an outcome that describes or reflects how a patient feels, functions or survives); a *ClinRO* is a measurement by a trained health care professional after observing a trial participant's health condition, a *PerfO* is a measurement based on a standardized task performed by a participant that is administered and evaluated by an appropriately trained individual or is individually completed, a *PRO* is a measurement based on a report that comes directly from the participant about the status of a patient's health condition without amendment or interpretation of the participant's response by a clinician or anyone else, and an *ObsRO* is a measurement based on a report of observable signs, events, or behaviors related to a participant's health condition by someone other than the participant or a health professional (e.g., a parent or caregiver). See FDA-NIH Biomarker Working Group BEST (Biomarkers, Endpoints, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016, available at https://www ncbi nlm.nih.gov/books/NBK326791/. Co-published by National Institutes of Health (US), Bethesda, (MD).

[37] Non-interview-based ClinRO assessments, such as those reliant on diagnostic imaging or physical examination, present a distinct set of challenges and are not addressed in this guidance.

should ensure that the methods and conduct of remote assessments are consistent across sites, trial participants, and visits to minimize variability in the data. For example, if a sponsor decides that video is their preferred method of remote assessment in a clinical trial, then using different methods to conduct assessments (e.g., both telephone and video in the same trial) may increase variability. Maintaining consistency in assessment methods should be balanced, however, against the need to minimize missing data and the decision to use different methods should be justified in study documentation.

Feasibility of the Assessment Method Within the Context of Use: Investigators should assess the feasibility of conducting a specific type of COA remotely, which will depend on corresponding trial goals and needs (e.g., ability to conduct the assessment in a way that captures all the data needed to evaluate the endpoint in the trial), given that not all assessments can provide an accurate assessment when done remotely.

Documentation and Audit Trails: Investigators should document, and sponsors should include data on related variables in the clinical trial datasets, whether an assessment was conducted in-person or remotely (including type of technology used), as well as the date of the assessment and the person who conducted the assessment. Sponsors also should ensure that remote data acquisition, transmission, and storage are secure, and that the privacy of trial participants is protected. When sponsors use electronic platforms to perform remote assessments that transmit data directly into trial records, these platforms should include automated audit trails.

Technology and Technological Support: Sponsors planning to use remote electronic assessments as part of a clinical investigation should use appropriate technology and develop procedures for provision of technology and technical support to trial participants, investigators, and/or other trial personnel to facilitate those assessments. For example, sponsors could develop a plan to accommodate trial participants who are either already enrolled in a trial or may be enrolled in a trial in the future, but who do not have access to appropriate communication technology (e.g., cell phones or Internet), by providing trial participants with these services.

Specific considerations for certain COA types are explained below.

PerfO- and Interview-Based ClinRO-Specific Considerations: For these types of assessments, sponsors should consider: (1) appropriateness of remote assessment for the type of clinical data to be collected; (2) special investigator training to administer the PerfO or interview-based ClinRO assessments remotely; and (3) procedures for assessing and confirming the safety of trial participants, their privacy, and appropriate setting and resources to adequately complete the assessment.

Recognizing that components of the PerfO and interview-based ClinRO assessment for some trials may specify visualization or in-person interactions with trial participants that may be difficult to replicate through remote interactions, sponsors should assess whether these components can be evaluated in an alternative way that still permits an accurate clinical assessment. When components of the assessment cannot be accomplished in a remote encounter, investigators should document, and sponsors should report in the clinical trial datasets, any aspects of the assessment they are unable to accomplish remotely. Sponsors should consider

whether the information that can be collected remotely will be sufficient to reliably assess the clinical outcome and support robust conclusions for the study.

PRO- and ObsRO-Specific Considerations: For these types of assessments, sponsors should consider: (1) potential for missing data when switching from in-person assessment to remote assessment; (2) whether switching from use of paper- or electronic-based PRO and ObsRO assessments completed independently to assessments administered verbally by another person may lead to bias of scores (e.g., if trial participants try to please the site staff by offering ratings that might not truly reflect their experience); and (3) that data collected with PROs and ObsROs through verbal administration should not be considered a substitute for required safety monitoring throughout the trial.[38]

To minimize potential bias resulting from verbal administration of PRO and ObsRO assessments, sponsors should ensure interviewer training and use of an interview script. Sponsors may also consider using automated virtual interviewers or a trained neutral third-party interviewer to administer the assessments remotely.

The potential for missing data is also a limitation when switching from in-person to remote assessment using paper-based PRO or ObsRO assessments, if the trial participant or observer fails to complete all or part of the questionnaire within a given timeframe. To mitigate potential for missing data, sponsors should consider remote electronic capture of these assessments through technologies that can remind trial participants to complete the questionnaires and/or verbal administration at the time instructed (assuming appropriate steps are taken to minimize bias from verbal administration).

Q15. I am a study monitor and am unable to conduct on-site monitoring visits due to the COVID-19 public health emergency. May I remotely perform the site monitoring visit? What recommendations does FDA have for how I can remotely perform source document review?

FDA regulations require sponsors to monitor the conduct and progress of their clinical investigations.[39] The regulations are not specific about how sponsors must conduct such monitoring and are therefore compatible with a range of approaches to monitoring that may vary depending on multiple factors. Therefore, certain aspects of site monitoring visits may be done remotely if technically feasible. FDA understands that there may be deviations from the timing of on-site monitoring visits set forth in the trial monitoring plan and procedures, and that sponsors may consider ways to replace on-site monitoring visits with remote monitoring visits during the COVID-19 public health emergency. Further, there may be components of an on-site monitoring visit, as outlined in the trial monitoring plan, that cannot be completed remotely.

During the COVID-19 public health emergency, traditional on-site monitoring might be difficult for reasons such as (1) sites may not be able to accommodate monitoring visits (e.g., due to staffing limitations or site closures) or (2) monitors may not be able to travel to trial sites. When

[38] See 21 CFR 312.32(b), 312.56(c), and 812.46.
[39] See 21 CFR 312.50, 312.53(d), 312.56(a), 812.40, 812.43(d), and 812.46.

planned on-site monitoring visits are not possible, the reason should be documented and available for review by the sponsor and during FDA inspections.

The sponsor should consider using a risk-based approach to prioritize sites for remote monitoring, including as many study sites as feasible (and with a frequency as close to that described in the site monitoring plan as feasible). The decision regarding which sites to prioritize for remote monitoring should be guided by centralized monitoring or other information available about site performance (e.g., frequency and severity of protocol deviations previously identified during monitoring visits or currently identified by centralized monitoring, number of randomized active trial participants, experience of site staff, known history of prior major audit or inspection findings).

Remote monitoring should be focused on review of critical study site documentation and source data. If the materials identified for review include participants' medical records that normally would be reviewed at the site (and such a review is consistent with the trial participants' informed consent documents) then, as discussed below, remote review of medical records may be explored with trial sites to complete source document review. When the study monitor cannot access the site to review critical source documents, requests for review of source documents that may include private health information should be consistent with requirements for source document validation and review as described in the current study monitoring plan or other appropriate study-specific document. When remote monitoring processes and procedures have not previously been described by the sponsor, these processes and procedures should be established (e.g., in a revised study monitoring plan or in updates to existing sponsor policies and procedures).

During remote monitoring, the study monitor should focus on trial activities that are essential to the safety of trial participants and/or data reliability. Sponsors and monitors may wish to consider one or more of the following options to facilitate remote monitoring access to clinical site records:

- If the site can provide appropriate resources and technical capabilities, consider establishing a secure remote viewing portal that would permit site staff to provide access to the site's study documentation and/or trial participants' source documents for the study monitor's review. In addition, the potential for remote access to trial participants' electronic health records may be explored with trial sites.

- Sites could upload certified copies[40] of source records to a sponsor-controlled electronic system or other cloud-based repository that contains appropriate security controls. In the setting of a blinded or partially blinded study, if source documents contain potentially unblind information, controls to protect the study blind should be in place prior to transfer of source documents (e.g., use of an unblinded study monitor to review source documents, restricted access to folders containing copies of source documents). It is not necessary for the clinical site to have control of certified copies of source documents uploaded to such a

[40] See footnote 26.

> repository; however, the clinical investigator should maintain control of the original source records.

Regarding retention of copies of source documents used for remote review, it would not be necessary to retain the certified copies of source documents used for remote review, provided the clinical investigator retains the original source documents according to FDA regulations for the retention of records.[41]

In addition, processes and procedures should be established for the handling of source document copies that were placed in temporary storage locations for remote review and that are no longer needed after the remote monitoring has concluded.

Remote monitoring activities, including remote review of source documents, should be documented in the same level of detail as on-site monitoring activities, and any resulting actions to address issues identified from the remote source document review should be consistent with procedures and processes described in the study monitoring plan.

Q16. I am a sponsor of commercial INDs and electronic common technical document (eCTD) requirements cannot be met due to the COVID-19 public health emergency. Who do I contact for assistance?

Commercial sponsors may qualify for a short-term waiver from the eCTD requirements under section 745A of the FD&C Act in unique and rare circumstances and for a limited duration. During the COVID-19 public health emergency, rare circumstances may arise in which a sponsor cannot meet eCTD requirements (e.g., if the current COVID-19 public health emergency has impacted computer operations). Companies experiencing technical difficulties with transmission of their electronic submissions to FDA should consult FDA's electronic submission staff (contact information provided below) for technical assistance, rather than submitting a waiver request, as described in Section III.E of FDA's guidance for industry *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (February 2020, Revision 7):

> FDA may grant temporary waivers of the requirement for eCTD submission if one or more of the following events or circumstances exist:
>
> - Extraordinary events or circumstances occur that are beyond the control of the submitter that justify a waiver, including but not limited to, natural disasters that impact computer operations.
> - An unplanned long-term Internet disruption or other unplanned event occurs that would preclude the sponsor from submitting in eCTD format (e.g., malware attacks).
> - The sponsor intends to request a withdrawal of an application that has not yet converted to eCTD format.

[41] See 21 CFR 312.62 and 812.140(a)

- The sponsor submitted a request for withdrawal and has not yet received FDA's acknowledgement of the withdrawal.[42]

The guidance also states:

> The sponsor or applicant's request to waive the eCTD electronic format requirement must include *all* of the following as supporting documentation to justify the waiver:
>
> (a) A description of the circumstances or event–including the anticipated duration of the circumstance or event–giving rise to the need for a waiver
>
> (b) The requested duration of the waiver
>
> (c) A description of the proposed alternative submission format the sponsor or applicant will be using for the duration of the waiver
>
> The request should reference all products that are to be covered by the waiver. The waiver request should be clearly titled "**WAIVER REQUEST–eCTD REQUIREMENTS**" in bold capital letters at the top of the first page of the submission.[43]

Waiver requests for new drug applications (NDAs), biologics license applications (BLAs), abbreviated new drug applications (ANDAs), drug master files (DMFs), and commercial INDs may be sent to FDA electronic submission staff via email to CDER [redacted] or CBER[redacted]. If a waiver is granted, FDA intends to provide information in the response letter on how to transmit the submission. FDA intends to encourage sponsors and applicants to send submissions electronically in an alternative electronic format (e.g., PDF files following the eCTD structure).

Q17. During the COVID-19 public health emergency, certain patients may no longer be able to travel to a central location for protocol-based treatment that is scheduled on a recurring basis. Can the investigational product intended for infusion be shipped to a local health care provider who is not a sub-investigator to administer the infusion to a patient while still maintaining integrity of the trial? If so, what else would be needed regarding trial monitoring and institutional review board (IRB) oversight?

Specific circumstances for a given clinical trial would affect the feasibility and appropriateness of shipping investigational products (IP) to locations other than clinical trial sites as specified under an IND, as well as administering the IP. If the IPs being evaluated in the trial are administered by infusion, then it would be important that any alternative infusion center have appropriately trained personnel and oversight by physicians with sufficient experience regarding

[42] See the guidance for industry *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (February 2020, Revision 7), available on the FDA guidance web page. To the extent that the guidance provides criteria for waivers and exemptions from the eCTD reporting requirements under section 745A(a) of the FD&C Act, it has binding effect pursuant to statute.
[43] Ibid.

the class of products involved to assure trial participant safety comparable to administration at a trial site.

For the purposes of this guidance, local health care providers (HCPs) who are administering drugs in a manner that does not differ from their normal clinical practices would not be considered sub-investigators and need not be listed on Form FDA 1572.[44] FDA recommends that these HCPs be listed in site records, such as a log of activities delegated by the investigator. Any changes to a trial protocol to permit an HCP to administer the investigational drug generally must be reviewed and approved by an IRB.[45]

The above paragraph described administration of the investigational product by local HCPs who are practicing medicine within their scope of practice. In contrast, if a sponsor will be asking local HCPs to perform study-specific research procedures or assessments that represent a direct and significant contribution to the clinical data for the study (e.g., assessing drug response for a patient or performing a procedure unique to the study and not part of routine medical care), these HCPs would be considered sub-investigators and should be listed on Form FDA 1572.

IP may be shipped from a central distribution site directly to an HCP, provided that such shipping is done under the supervision of the investigator using procedures that assure accountability and product quality (i.e., that storage conditions, as defined in the protocol, for the IP were maintained during shipping, and the drug packaging was intact upon receipt).

If the HCP administering the IP is not considered a sub-investigator, the investigator should ensure that they can obtain records regarding administration of the IP by requesting that the trial participants provide consent to allow access to medical records from their local HCPs involving trial-related data such as measuring vital signs, and results of evaluations of any symptoms or signs occurring with the infusion. Communicating the intent to request such records from the HCP in advance may facilitate this process.

Consulting the appropriate FDA review division(s) on plans for alternative administration is also recommended as per Q9 above.

Q18. If a trial participant is unable to receive the investigational drug from the trial site but the product is FDA-approved for other uses, can the patient or health care provider secure the product commercially or is this considered the sponsor charging for the investigational drug under 21 CFR 312.8? Can the sponsor reimburse trial participants for their out of pocket expenses in getting the drug commercially?

If the product(s) under investigation in a clinical trial is FDA-approved, and the study does not require blinding, then local sourcing of the product(s) would be acceptable to FDA (e.g., by having the local physician write a prescription for the product instead of shipping the product

[44] For the definition of a *sub-investigator*, see 21 CFR 312.3(b); for the requirement to list sub-investigators on the FDA Form 1572, see 21 CFR 312.53(c)(1).

[45] As noted in the response to Q3 above, changes to a protocol necessary to eliminate an apparent immediate hazard to trial participants may be implemented before FDA and IRB review and approval (see 21 CFR 56.108(a)(4) and 21 CFR 312.30(b)(2)(ii)).

directly to the patient). FDA does not consider a trial participant's commercial procurement of the study drug when unable to secure it from the trial site during the COVID-19 public health emergency to be a sponsor charging for an investigational drug under an IND per FDA regulations at 21 CFR 312.8. FDA also would not object if the sponsor reimburses the patient for any costs incurred by commercially purchasing the product or for charges related to an infusion.

Per FDA regulations at 21 CFR 312.6, the immediate package of an investigational new drug intended for human use must bear a label with the statement "Caution: New Drug—Limited by Federal (or United States) law to investigational use." FDA recognizes that a commercially obtained product will not have this statement on its container. In the setting of the COVID-19 public health emergency, where alternative arrangements are being made to provide an investigational agent to a participant who is unable to come to the trial site, FDA intends to exercise flexibility without sponsors needing to seek a waiver under 21 CFR 312.10 of the investigational labeling requirements under 21 CFR 312.6.

Q19. Throughout the guidance, FDA recommends that sponsors consult with the review division for certain changes to ongoing clinical trials. For drugs and biologics, is this a reference to scheduling a Type A meeting? How should sponsors contact FDA regarding device clinical trials?

As stated in our guidance for industry *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* (December 2017),[46] review division regulatory project managers (RPMs) are the primary point of contact for communications between a sponsor and FDA. Both FDA and sponsors use various communication methods to focus discussions to exchange information and resolve issues efficiently. For example, telephone communication between a sponsor and FDA RPM may be more effective for time-sensitive matters. FDA staff try to respond to sponsor questions promptly, while balancing FDA public health priorities and other work obligations. Note that to ensure participant safety, responses to safety-related inquiries will be prioritized over other inquiries. More generally, FDA understands that many questions that will arise regarding changes in trial conduct due to COVID-19 will need to be addressed expeditiously. RPMs will work with sponsors to determine the best path forward to answer their questions for certain changes in an expedited manner.

To discuss urgent issues related to IDEs managed in CDRH, sponsors should contact the lead reviewer. For IDEs managed in CBER, sponsors should contact the RPM. For FDA feedback on a proposed future IDE study, or regarding modifications to ongoing studies that are not urgent (such as a statistical analysis plan to address missing data), a Pre-Submission is recommended. For additional information on Pre-Submissions, please refer to FDA's guidance for industry *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program* (May 2019).[47]

For general questions regarding FDA policy on clinical trial conduct during the COVID-19 public health emergency, sponsors should contact [redacted]

[46] Available on the FDA guidance web page.
[47] Available on the FDA guidance web page.

Q20. I am a sponsor and would like to use an alternate laboratory or imaging center[48] for protocol assessments. What should I consider regarding when this approach would be appropriate and the selection of alternate laboratories or imaging facilities?

Given that trial participants may not be able to come to the investigational site for protocol-specified visits at which laboratory tests or imaging would be conducted, sponsors should evaluate whether it is feasible to use alternative laboratories or imaging centers. The suitability of such alternative arrangements may vary depending on whether the protocol-specified procedures are related to eligibility criteria, safety evaluations, or endpoint assessments.

In general, if trial participants cannot access a clinical trial site, alternative sites may be used for laboratory tests or imaging assessments that focus on the safety of trial participants when such tests and assessments are routinely performed in those settings (e.g., routine chemistries, blood counts, chest radiographs).[49]

However, if the results of laboratory tests or imaging assessments are the basis for formal hypothesis testing, including primary or secondary efficacy endpoints and some safety endpoints, sponsors should consult with the relevant FDA review division. For example, disparities in laboratory measurements or imaging protocols will introduce increased variability and thus can affect type I and type II error rates.

When baseline tests are necessary to characterize the eligible study population, potential variation in test performance or precision related to use of an alternative laboratory or imaging center may also warrant discussion with the FDA review division. For example, an inclusion criterion based on a commonly available, routine test performed as a safety screen (e.g., renal function on a metabolic panel) might be amenable to alternative laboratory collection with minimal impact on study results. Using an alternative laboratory for tests related to other eligibility factors could be more likely to affect study integrity (e.g., laboratory tests to identify a tumor biomarker required for inclusion, genetic test to identify a marker that is a critical inclusion criterion). It may be important for such assessments to be standardized at a single site or at most a few sites. Based on the nature of laboratory tests conducted for the purpose of protocol assessments, the alternative laboratory conducting such tests for investigational purposes will likely be subject to certification and other requirements under the Clinical Laboratory Improvement Amendments (CLIA).[50] Alternative laboratory and imaging centers may also be subject to additional laws governing their operations.

Q21. We are instituting trial participant visits remotely through video conferencing. Are there recommendations regarding best practices?

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[48] For IND studies, this would be laboratories and imaging centers not listed on the Form FDA 1572.

[49] If a local laboratory or imaging center will be used for certain patients and will not replace the laboratory and imaging center specified in the Form FDA 1572 for all patients, these alternative facilities do not need to be listed on the Form FDA 1572; it is sufficient to retain documentation of when such facilities were used for protocol specified tests. The sponsor can accumulate these changes and submit this information to the IND, in for example, an information amendment or a protocol amendment.

[50] For more information on CLIA, see https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/Research-Testing-and-CLIA.pdf.

With the increasing use of telemedicine in clinical practice, a number of resources may be available to provide recommendations on best practices. FDA does not endorse any particular telemedicine best practices. However, from an FDA regulatory perspective, important considerations for trial visits through video conferencing include:

- The investigator or study personnel who will conduct remote visits should be trained on how to conduct real-time video conferencing visits (e.g., training on the use of telemedicine for remote clinical trial visits).

- Procedures should be put in place to maintain a trial participant's privacy, as would be done for a clinical visit.

- Both the investigator and the trial participant should confirm their respective identities with one another before engaging in a real-time video conference visit according to an identity verification plan developed by the sponsor.[51]

To provide the same information that would be documented during a face-to-face visit, the date of a real-time video conference visit should be documented in the trial records and, if specified in the protocol, the time of the visit. Investigators should consider asking for the trial participant's location during a video conference visit in case a medical emergency arises during the visit.

FDA considers real-time video interactions, including telemedicine, as a live exchange of information between the trial personnel and trial participants. These interactions are not considered electronic records and therefore are not subject to 21 CFR part 11.

Q22. How does the COVID-19 public health emergency affect drug and biological product clinical trials required as postmarketing requirements (PMRs)? What about for required postmarket device studies?

The information in this guidance applies to all clinical trials, including those postmarketing clinical trials that FDA requires an applicant[52] to conduct[53] for drugs and biological products. Many of the considerations outlined in this guidance may also be relevant to postmarket device studies.[54]

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[51] FDA does not endorse any specific identification method. Sponsors may consider the National Institute of Standards and Technology (NIST) Digital Identity Guidelines, Special Publication 800-63A—Enrollment and Identity Proofing Requirements When Developing an Identity Verification Plan, available at https://pages.nist.gov/800-63-3/sp800-63a html.

[52] After a company submits a marketing application (e.g., new drug application (NDA), biologics license application (BLA), premarket approval application (PMA), De Novo Classification Request, or premarket notification (510(k)) for review, the company is referred to as the *applicant*. The person who initiates a clinical investigation is referred to as the *sponsor* (see 21 CFR 312.3 and 812.3(n)).

[53] Specifically, this response is intended to apply to studies or clinical trials required under 505(o)(3) of the FD&C Act (21 U.S.C. 355(o)(3)), confirmatory trials for drugs approved under the accelerated approval pathway (21 U.S.C. 356(c)(2)(A)) and deferred pediatric studies (21 U.S.C. 355B).

[54] For devices subject to PMA, FDA may require post-approval studies as a condition of approval (21 CFR 814.82(a)(2)). FDA may also require manufacturers to conduct postmarket surveillance studies of certain class II and class III devices under section 522 of the FD&C Act (21 U.S.C. 360l).

Applicants who are required to complete postmarketing clinical trials for drugs or biological products follow a timetable that includes due dates for completing certain milestones in the trial. FDA encourages applicants to inform FDA as soon as possible if they experience COVID-19-related delays that may affect the applicant's ability to meet the applicable interim,[55] trial completion, and/or final report submission milestone(s). These applicants should propose feasible revised milestones for interim, trial completion, and/or final report submission milestone(s).[56]

For post-market device studies, the approved post-approval study protocol or post-market surveillance plan generally includes due dates for completing certain study milestones. Due dates for certain milestones may also be listed expressly in the order requiring the postmarket study. Applicants required to complete such studies should similarly inform FDA as soon as possible of COVID-19-related delays that may affect the applicant's ability to meet those milestones and propose feasible revised milestones.

Applicants with PMRs or required postmarket device studies should also provide an explanation to FDA of how COVID-19 impacts the ability to meet the original milestones. FDA will evaluate the facts and circumstances of the explanation provided, as well as the conduct of the applicant, in determining whether the applicant is in compliance with the applicable authority requiring the postmarketing trial or postmarket device study after the milestone has been missed.

Additional considerations for drug and biological product PMRs include:

- **PMRs Under Section 505(o)(3) of the FD&C Act**. FDA will continue to make "good cause" determinations on a case-by-case basis for all missed milestones, including those where the applicant asserts that its failure to meet a PMR interim, trial completion, and/or final report submission milestone(s) is related to the current public health emergency.

- **Deferred Pediatric Study PMRs Under the Pediatric Research Equity Act (PREA).**[57] If circumstances involving COVID-19 have affected an applicant's ability to complete a PREA PMR, applicants may request a deferral extension for the final report submission milestone. If an applicant has not obtained a deferral extension and fails to submit required PREA studies by the final report submission date listed in the PREA PMR, FDA is required to issue a non-compliance letter to the applicant.[58]

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[55] *Interim milestones* refer to those due dates scheduled to occur between the final protocol submission and trial completion milestones.

[56] Although a revised trial completion date may be acknowledged by FDA, for drugs and biological product PMRs, the original projected completion date will continue to be displayed on the FDA's Postmarket Requirements and Commitments web page.

[57] Section 505B(a)(3)(B) of the FD&C Act governs the process and timelines required for requests for a deferral extension for deferred pediatric studies required under section 505B of the FD&C Act (21 U.S.C. 355c) (often referred to as *PREA PMRs*).

[58] See section 505B(d)(1) of the FD&C Act (21 U.S.C. 355c(d)(1)).

- **PMRs Under Accelerated Approval**. For confirmatory trials, if an applicant misses an interim, trial completion, and/or final report submission milestone, FDA will review the applicant's explanation for the delay, as well as assess the trial's progress prior to the current public health emergency, before determining whether or not the applicant has been compliant with its milestone obligations.

- **Annual Status Reports of PMRs**. Applicants must continue to follow the annual reporting requirements for PMRs[59] and should document in their annual status report the COVID-19-related reason(s) for missing interim, trial completion, and/or final report submission milestone(s), and any steps taken to address COVID-19-related factors.

Q23. My company is the NDA holder of an FDA-approved drug for a non-COVID-19 indication and is also the sponsor of an IND for the same drug being investigated to treat COVID-19. If I receive a spontaneous report of a serious adverse event that occurred with the approved drug being used in clinical practice for treatment of COVID-19, do I report that event to the IND for the COVID-19 investigational use?

Reports of serious adverse events (SAE) that occur *in clinical practice* with the use of an approved drug or biological product, whether or not the use is included in the labeling for that product, must be reported in accordance with the applicable post-marketing reporting requirements under FDA regulations at 21 CFR 314.80 and 600.80. Reports of SAEs for approved vaccines are submitted to the Vaccine Adverse Events Reporting System (VAERS), while reports of SAEs for other approved drugs and biological products are submitted to the FDA Adverse Event Reporting System (FAERS).[60]

Serious adverse events that occur *during a clinical trial* under an IND for an approved drug or biological product being investigated for a new use to treat COVID-19 must be reported as an IND safety report per FDA regulations at 21 CFR 312.32 if they are unexpected *and* the sponsor determines that there is a reasonable possibly that the drug caused the SAE.

Regardless of whether an SAE occurs in the course of clinical practice or during a clinical trial, and regardless of where it is first reported, an NDA or BLA holder who is also the sponsor of an IND investigating the same drug for COVID-19 is responsible for monitoring the safety of its drug and evaluating all accumulating safety data.[61] If accumulating safety data, including use in clinical practice, indicates a new serious risk associated with the drug, an IND safety report will need to be filed to the IND, and updates will likely need to be made to the investigator brochure and/or the informed consent document.[62] For more information, see FDA's guidance for

[59] See section 506B of the FD&C Act (21 U.S.C. 356b), 21 CFR 314.81(b)(2)(vii), and 601.70(b).

[60] For more information, see the Vaccine Adverse Event Reporting System, available at https://vaers hhs.gov/reportevent html, and the FDA Adverse Event Reporting System (FAERS) Public Dashboard, available at https://www fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard.

[61] See 21 CFR 312.32(b).

[62] See 21 CFR 312.32(c).

industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012).[63]

Q24. For a clinical trial that is *not investigating treatments for COVID-19*, if a trial participant diagnosed with COVID-19 experiences a serious adverse event associated with COVID-19 during the trial, should that be reported as an IND safety report? Should these events be reported to the IRB?

Under FDA regulations at 21 CFR 312.32, a sponsor must report to FDA any serious adverse event (SAE) that is both unexpected and for which there is a reasonable possibility that the drug caused the serious adverse event, i.e., there is evidence to suggest a causal relationship between the drug and the adverse event.

Given the community spread of infection during the COVID-19 public health emergency, trial participants in a clinical trial may be diagnosed with COVID-19 and experience SAEs associated with the disease that are not causally related to the investigational drug. However, it also is possible that an investigational drug might be causally related to a SAE associated with COVID-19 by making trial participants in the trial more susceptible to complications from COVID-19. Establishing this potential causal relationship likely requires more than a single or even a few cases. To determine whether a reasonably possible causal relationship exists between an investigational drug and an SAE in a randomized controlled trial, FDA recommends a comparison between the rate of observed SAEs among COVID-19 infected trial participants in the investigational drug arm to COVID-19 infected trial participants in the control arm. Given that such analyses entail examination of unblinded data, such assessments should be done only by a data monitoring committee that routinely reviews unblinded data or by a specially constituted safety committee that is appropriately "firewalled" and independent from those conducting the trial and performing other study analyses. If the latter, such a committee should review safety data only, not efficacy data. If the trial is not randomized, in some circumstances it may be warranted to determine whether there is an excess of SAEs in trial participants diagnosed with COVID-19 by comparing the rate of such events to an external similar population diagnosed with COVID-19, recognizing that the reported rates of SAEs and mortality in patients with COVID-19 have varied widely. In comparing the rate in the trial to the published literature, sponsors should consider reports in patients with similar comorbidities and levels of care. If the difference in SAEs across treatment arms or compared to an external population suggests a causal relationship between the investigational product and the SAEs in trial participants diagnosed with COVID-19, this finding must be submitted to FDA as an IND safety report in accordance with 21 CFR 312.32.

FDA had provided additional information about aggregate safety assessment and reporting for INDs in the guidance for industry and investigators, *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012),[64] and has proposed recommendations in the draft guidance for industry *Safety Assessment for IND Safety Reporting* (December 2015).[65]

[63] Available on the FDA guidance web page.
[64] Available on the FDA guidance web page.
[65] Available on the FDA guidance web page. When finalized, this guidance will represent FDA's current thinking on these issues.

Where an IND safety report is required to be submitted to FDA under 21 CFR 312.32, the investigator must also send that IND safety report to the IRB.[66] The IRB may have additional reporting requirements regarding COVID-19 during the clinical trial.

Q25. Trial participants with COVID-19 may experience a number of serious and unexpected adverse clinical events, which may increase the volume of corresponding IND safety reports. If an investigator receives an IND safety report from a sponsor, is it acceptable to review only reports that the sponsor indicates will result in a change to the investigator brochure, informed consent, or protocol? Which IND safety reports must an investigator send to the IRB?

No, it is not acceptable for an investigator to review only certain IND safety reports. Under 21 CFR 312.60, investigators are responsible for protecting the safety of trial participants in a clinical investigation. IND safety reports must be sent by the sponsor to FDA and all participating investigators[67] when the sponsor determines that a serious adverse event is unexpected and there is a reasonable possibility that the drug caused the serious adverse event, i.e., there is evidence to suggest a causal relationship between the drug and the adverse event.[68] Reviewing IND safety reports is essential for protecting the safety of trial participants because a serious and unexpected adverse event represents a new potential risk associated with the investigational product. FDA considers the review of all IND safety reports critical to fulfilling investigators' responsibility to protect the safety of trial participants in a clinical investigation.[69]

In addition, investigators are required under 21 CFR 312.66 to report all "unanticipated problems involving risk to human subjects or others" to the IRB. FDA considers a serious and unexpected adverse event that meets the criteria for sponsor reporting to FDA and all investigators in an IND safety report under 21 CFR 312.32, and would generally consider a serious adverse event that meets the criteria for safety reporting for an IND-exempt bioavailability/bioequivalence study under 21 CFR 320.31(d)(3), to be an "unanticipated [problem] involving risk to human subjects or others" that therefore must be reported to the IRB by the investigator.[70,71]

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[66] See 21 CFR 312.53(c)(1)(vii) and 312.66. See also the guidance for clinical investigators, sponsors, and IRBs *Adverse Event Reporting to IRBs—Improving Human Subject Protection* (January 2009), available on the FDA guidance web page.

[67] See 21 CFR 312.32(c)(1).

[68] See 21 CFR 312.32. IND safety reports must be submitted as soon as possible, but no later than 15 calendar days after the sponsor determines that the information qualifies for reporting. Unexpected fatal or life-threatening suspected adverse reactions must be submitted no later than 7 calendar days after the sponsor's initial receipt of the information (21 CFR 312.32(c)(2)).

[69] See 21 CFR 312.60.

[70] See 21 CFR 312.66.

[71] Many study protocols specify that the sponsor will submit IND safety reports to the IRB on the investigator's behalf. In these situations, where the investigator receives confirmation that the report has been sent to the IRB (e.g., the investigator is copied on the report sent to the IRB by the sponsor), FDA does not intend to object to the sponsor submitting the report to the IRB on the investigator's behalf and would not expect an investigator to provide the IRB with a duplicate copy of the report.

For more information about safety reporting, see FDA's guidances *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012)[72] and *Adverse Event Reporting to IRBs—Improving Human Subject Protection* (January 2009).[73]

Q26. What considerations apply to the electronic systems used to generate electronic signatures on clinical trial records, including informed consent documents, during the COVID-19 public health emergency?

Electronic systems[74] used to generate electronic signatures[75] on clinical trial records, including informed consent documents, during the COVID-19 public health emergency must comply with the requirements outlined in FDA regulations at 21 CFR part 11 (Part 11) when applicable.[76, 77]

FDA is aware that there are multiple commercial off-the-shelf (COTS) software systems providing electronic signature services for clinical trial records. FDA does not certify individual electronic systems or methods to obtain Part 11 compliant electronic signatures, but COTS vendors may be able to provide sponsors and other regulated entities with information regarding whether their systems are Part 11 compliant. When such information is unavailable from the vendor, and a Part 11 compliant electronic system is required, sponsors and other regulated entities must take other steps to ensure the electronic system or software in use is Part 11 compliant. For further information regarding Part 11 compliance, see FDA's guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application* (August 2003)[78] and the additional recommendations proposed in the draft guidance for industry *Use of Electronic Records and Electronic Signatures in Clinical Investigations under 21 CFR Part 11—Questions and Answers* (June 2017).[79]

When an electronic system that is Part 11 compliant is not available, regulated entities must have an alternate means of obtaining required signatures (e.g., handwritten[80] wet ink signatures executed on documents, handwritten stylus or finger-drawn signatures executed on electronic documents that are then printed or appropriately witnessed). Alternative methods for obtaining signatures on informed consent documents during the COVID-19 public health emergency are described in Q11 and Q12 of this guidance. When handwritten methods are used, the sponsor and other regulated entities should ensure that all records containing original handwritten signatures are (1) collected and archived, as either original paper copies or appropriately certified

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[72] Available on the FDA guidance web page.
[73] Available on the FDA guidance web page.
[74] For the purposes of this guidance, the term *electronic systems* means systems, including hardware and software, that produce electronic records.
[75] For the purposes of this guidance, the term *electronic signature* means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature (21 CFR 11.3(b)(7)).
[76] See 21 CFR 11.1(b). See also the guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application* (August 2003), available on the FDA guidance web page.
[77] For records that are not subject to Part 11, sponsors and other regulated entities should rely on their internal business practices to determine acceptable electronic signature methods and controls.
[78] Available on the FDA guidance web page.
[79] Available on the FDA guidance web page. When final, this guidance will represent FDA's current thinking on this topic.
[80] See 21 CFR 11.3(b)(8) for the definition of a *handwritten signature*.

electronic copies (e.g., using a validated process for scanning paper copies), and (2) retained according to applicable FDA record retention requirements.[81]

Q27. Certain clinical trial protocols have an exclusion criterion for receipt of another "investigational medical product." If a participant receives a vaccine or other medical product for the prevention or treatment of COVID-19 authorized under an Emergency Use Authorization (EUA), would FDA consider this receipt of an investigational medical product?

When a medical product is being used under an EUA, it is an authorized (though not an approved or cleared) medical product for use in clinical care that has met the statutory criteria under section 564 of the FD&C Act. The product is not being studied under an IND or IDE when used pursuant to an EUA, and FDA therefore does not consider receipt under an EUA as receipt of an investigational product.[82] In contrast, when the same product is used in a clinical investigation under an IND or IDE, the product's safety and/or effectiveness is being studied for investigational uses, and FDA would consider receipt in this situation to be receipt of an investigational product.

As always in the design of a clinical investigation, there may be valid scientific reasons to have an exclusion (and even a discontinuation) criterion for a medical product—a monoclonal antibody or vaccine, for example—whether that product was used under an EUA or not. These scientific reasons may include risks to an individual if they enroll or continue to participate in a clinical trial after receiving (or having received) the excluded product, or the potential impact of the use of the excluded product on trial objectives, such as confounding the determination of effectiveness of the product under investigation.

[81] See 21 CFR 312.57, 312.62, and 812.140.

[82] See guidance for industry *Emergency Use Authorization of Medical Products and Related Authorities* (January 2017), available on the FDA guidance web page.

Q28. During the COVID-19 public health emergency some sponsors have used remote monitoring to oversee study conduct at clinical trial sites, including remote review of source data. Should data that have been remotely monitored be re-monitored during an on-site monitoring visit once pandemic-related restrictions that prevented on-site monitoring visits have been lifted?

FDA regulations require sponsors to monitor the conduct and progress of their clinical investigations.[83] These regulations are not specific about how sponsors must conduct such monitoring and are therefore compatible with a range of approaches that may vary depending on multiple factors. FDA's guidance for industry *Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring* (August 2013) clarifies that sponsors can use a variety of approaches to fulfill their responsibilities for monitoring clinical investigations; the guidance also describes monitoring activities that reflect modern, risk-based approaches, including remote monitoring when appropriate.

The decision as to whether remote monitoring conducted for a given site or clinical investigation was adequate or should be followed up with additional on-site monitoring visits should be based on the sponsor's ongoing risk assessment. The sponsor may determine that on-site follow-up of remote monitoring activities is appropriate based on a risk assessment (e.g., sites with certain data anomalies or a higher frequency of errors, important protocol violations, or dropouts relative to other sites). As with on-site monitoring, remote monitoring should be focused on critical data and processes for human subject protection and trial integrity, such as the site's conduct of key study procedures and documentation related to important efficacy endpoints and safety assessments.

[83] See 21 CFR 312.50, 312.53(d), 312.56(a), 812.40, 812.43(d), and 812.46.

GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC

Version 4

04/02/2021

Key changes from v3 (27-04-2020): remote source data verification

Commission européenne/Europese Commissie, [redacted] - Tel. [redacted]
Office: [redacted] - Tel. direct line [redacted]

CONTENTS

The European Medicines Agency (EMA), Good Clinical Practice (GCP) Inspectors Working Group (GCP IWG), the Clinical Trials Facilitation and Coordination Group (CTFG, a working group of the Heads of Medicines Agency (HMA), the Clinical Trials Expert Group (CTEG, a working group of the European Commission representing Ethics Committees and National Competent Authorities (NCA)) and the European Commission (EC) acknowledge the impact of COVID-19 on the health system and broader society, and the impact it may have on clinical trials and trial participants[1]. Extraordinary measures may need to be implemented and trials adjusted due, among others, to trial participants being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infection, and health care professionals being committed to critical tasks.

The COVID-19 pandemic is rapidly escalating putting national health care systems under continuously increasing pressure. In some Member States the capacity of the health-care system has already reached its limits. Against this background, pragmatic and harmonised actions are required to ensure the necessary flexibility and procedural simplifications needed to maintain the integrity of the trials, to ensure the rights, safety and wellbeing of trial participants and the safety of clinical trial staff during this global public health crisis. The points mentioned below are intended to provide guidance and clarity for all parties involved in clinical trials during this time. **It should be noted that the simplification measures proposed in this document will only last during the current public health crisis until the revocation of this Guidance, when there is a consensus that the period of the COVID-19 outbreak in the EU/EEA, has passed.**

Sponsors[2] and investigators should note that due to the rapidly evolving situation further updates to this guidance are possible and likely.

Member States are encouraged to implement the harmonised guidance to the maximum possible extent to mitigate and slow down the disruption of clinical research in Europe during the public health crisis. At the same time, sponsors and investigators need to take into account that national legislation and derogations cannot be superseded. Member States shall complement this guidance to create additional clarity on specific national legal requirements and derogations to them[3].

This document sets out to include most of the current guidance across Member States with the aim of serving as a harmonised EU-level set of recommendations. Hence, this guidance was drafted and supported by the CTEG, EMA, the CTFG of the HMA and the GCP IWG coordinated by the EMA. Commissioner Kyriakides shared this guidance with the Health Ministers and no Member State has raised any concern with this guidance in the videoconference of Ministers of Health of 27 April 2020.

1. INTRODUCTION

Various challenges exist which result in restrictions of visits to healthcare facilities, increased demands on the health service and changes to trial staff availability. Trial

[1]The word "trial participant" is used in this text as a synonym for the term “subject”, defined in Directive 2001/20/EC as “an individual who participates in a clinical trial as a recipient of the investigational medicinal product or a control”.

[2]Sponsors should be read in this context as ”sponsor and/or CRO”.

[3]Links to national guidance documents are collected here: https://www hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_03_CTFG_Link_to_National_guidance_on_CT_managmant_during_the_COVID-19_pandemia.pdf

participants may also be required to self-isolate, which can make it difficult for investigators to maintain their medical oversight. These challenges could have an impact on the conduct of trials, such as the completion of trial assessments, completion of trial visits and the provision of Investigational Medicinal Products (IMPs).

The impact of COVID-19 on ongoing trials, on opening new trial sites in an existing trial, on ongoing recruitment and continued involvement of participants in the trial, or on starting of new trials needs to be considered. This evaluation should take into account national recommendations and measures including travel restrictions and confinements of trial participants and trial staff and the availability of trial staff to perform visits, enter data in the Case Report Form (CRF), notify serious adverse events and, more generally, follow the protocol. The ability to confirm eligibility and to conduct key safety assessments and trial evaluations is of particular importance.

Actions should be proportionate and based on benefit-risk considerations, on contingency provisions taken nationally and locally by the authorities, with priority given to the impact on the health and safety of the trial participant. Where a trial participant is unable to attend the site, other measures, such as home nursing, if possible given social distancing needs, or contact via phone or telemedicine, may be required to identify adverse events and ensure continuous medical care and oversight. However, the limitations and risks of such methods and the requirements for data protection should be taken into account and such alternative arrangements need to be adequately documented.

The International Committee of Medical Journal Editors has made clear that in the event of public health emergencies, information with immediate public health implications should be disseminated without concern that this will preclude subsequent consideration for publication in a journal.[4]

2. INITIATING NEW TRIALS

The feasibility and immediate necessity of starting a new clinical trial should be critically assessed by sponsors, in close collaboration with other relevant parties, in particular the investigators. Additional risks to trial participants should be addressed in the benefit-risk section of the protocol along with risk mitigation measures (see chapter 5).

3. CHANGES TO ONGOING TRIALS

Sponsors should consider in their risk assessment whether the following measures could be the most appropriate during COVID-19. Measures should generally be agreed with investigators and could be:

- Conversion of physical visits into phone or video visits, postponement or complete cancellation of visits to ensure that only strictly necessary visits are performed at sites;

- A temporary halt of the trial at some or all trial sites;

[4] http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/overlapping-publications html

- Interruption or slowing down of recruitment of new trial participants – the feasibility of including new trial participants in an ongoing trial needs to be critically assessed;

- Extension of the duration of the trial;

- Postponement of trials or of activation of sites that have not yet been initiated;

- Closing of sites. In case it is not feasible for a site to continue participation at all, the sponsor should consider if the trial site should be closed and how this can be done without compromising the rights, safety and well-being of trial participants and data validity;

- If unavoidable (it should be justified that this is a truly exceptional situation based on the personal benefit-risk ratio for the individual trial participant), transfer of trial participants to investigational sites away from risk zones, or closer to their home, to sites already participating in the trial, or new ones, could occur. Initiation of new trial sites is generally not expected in the current situation unless no other solution exists for the trial participant. If there is an urgent need to open a new trial site for critical trial visits, for example outside the hospital, this may be implemented as an urgent safety measure (USM) first, followed later by a substantial amendment (SA) application (see below in chapter 6) for the approval and initiation of this additional site. In such cases, it is important that trial participants as well as investigators (both receiving and sending) are in agreement about the transfer, that the receiving site has the possibility to access previously collected information/collected data (including necessary medical records) for the trial participant and that any eCRF can be adjusted accordingly to allow the receiving site to enter new data. The impact on trial participants should be considered and arrangements made such as providing adequate transportation;

- There may be a need for critical laboratory tests, imaging or other diagnostic tests to be performed, (e.g. blood cell count, liver function test, X-ray, CT, MRI, ultrasonography, ECG etc.), e.g. for trial participant safety or the integrity of the trial. In case the trial participant cannot reach the site to have these performed, it is acceptable that laboratory, imaging or other diagnostic tests are done at a local laboratory or relevant clinical facility authorised/certified (as legally required nationally) to perform such tests routinely, if this can be done within local restrictions on social distancing. The sites should inform the sponsor about such cases. Local analysis can be used for safety decisions.

  If this is a trial endpoint and biological samples cannot be shipped to the central laboratory, analysis should be performed locally and then explained with detailed justification, assessed and reported in the clinical study report following ICH E3. In these cases, it is important that the sponsor is given access to the normal ranges and certification information of any additional laboratory used in order to support the use and evaluation of results.

The changes above may also be initiated by the investigator sites contacting the sponsor. There might also be cases where the current principal investigator (PI) of a site is

indisposed for a period and may need to delegate parts of his/her duties temporarily to e.g. a sub-investigator. Any permanent changes in PI should be submitted to the NCA and/or Ethics Committees (in line with chapter 6).

When changes in ongoing trials are considered, the overall well-being and best interests of the trial participants have to be prioritised, for example in trials for patients with life-threatening or severely debilitating conditions, when trial participants need to stay on trial treatment. When a trial is halted, even if temporarily only, this can potentially compromise the overall well-being and best interest of trial participants. All measures need to be considered and taken to avoid this.

Changes should be well balanced and proportionate, taking into account in particular the legitimate interest of trial sites in avoiding further burden in terms of time and staffing during the COVID-19 pandemic. Alternative arrangements, consistent with the protocol to the extent possible, should be fully documented with a well-reasoned rationale as to how they will ensure trial participant safety, data integrity and protection of personal data.

Please note that prospective protocol waivers remain unacceptable and that potential trial participants should not be included in trials without proper eligibility assessment, including performance of planned tests, and written informed consent according to national laws and regulations.

Compliance with the trial protocol should be ensured to such an extent that an ongoing benefit-risk assessment for the clinical trial and its participants is still possible. The impact of protocol changes on clinical data interpretability needs to be properly assessed by the sponsor and the overall evidence generation package could be subsequently discussed within scientific advice with regulatory authorities. A relevant guidance on the implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials by the CHMP Biostatistics Working Party was published on 25 March 2020[5].

4. SAFETY REPORTING

Sponsors are expected to continue safety reporting in adherence to EU and national legal frameworks (Directive 2001/20/EC[6]; CT-3[7]). When per protocol physical visits are reduced or postponed, it is important that the investigators continue collecting adverse events from the trial participant through alternative means, e.g. by phone calls or telemedicine visits, as appropriate.

5. RISK ASSESSMENT

The safety of the trial participants is of primary importance, and risks of involvement in the trial, in particular with added challenges due to COVID-19, should be weighed against anticipated benefit for the trial participants and society (ref: principle 2.2 of ICH GCP).

[5] https://www.ema.europa.eu/en/implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical-trials

[6] Directive 2001/20/EC (OJ L 121, 1.5.2001) https://ec.europa.eu/health/documents/eudralex/vol-10_en

[7] Communication from the Commission ('CT-3'; 2011/C 172/01) https://ec.europa.eu/health/documents/eudralex/vol-10_en

All decisions to adjust clinical trial conduct should be based on a risk assessment by the sponsor (ICH GCP section 5.0). It is expected that the sponsor performs a risk assessment of each individual ongoing trial and the investigator of each individual trial participant and implement measures, which prioritise trial participant safety and data validity. **In case these two conflict, trial participant safety always prevails.**

These risk assessments should be based on relevant parties' input and should be documented on an ongoing basis. It is important that sponsors in their risk assessment consider prioritisation of critical tasks in the clinical trial and how these are best maintained.

The sponsor should reassess risks as the situation develops. This reassessment should also be documented as part of the sponsor's trial master file.

It is possible that, with the escalation of the pandemic, local circumstances lead to a local change in risk assessment, therefore the need to implement additional measures may arise, and an investigator-driven risk assessment might be necessary. This assessment should be documented in the investigator's site master file and communicated to the sponsor.

The potential impact of COVID-19 on trial participants who may be determined as being part of a-risk group for COVID-19 or who are in trials involving treatments, which may increase such risks, should be carefully considered when deciding to start or continue such clinical trials.

6. COMMUNICATION WITH AUTHORITIES

Priority is given to any (new) clinical trial application for the treatment or prevention of COVID-19 infection, and/or substantial amendment applications to existing clinical trials necessary as a result of COVID-19.

For ongoing trials, the guidance given by EC CT-1[8] on substantial amendments remains applicable. A single submission by the same sponsor with the list of concerned trials and an aggregated list of changes is acceptable and encouraged in case of substantial amendments as well as of urgent safety measures.

Two important aspects need to be taken into account:

1) It is up to the sponsor to assess whether an amendment is to be regarded as 'substantial'. A change is substantial when it has a potential impact on the safety or physical or mental integrity of the clinical trial participant, or on the scientific value of the trial (CT-1 section 3.3, CT-2 section 5[9]). Substantial amendments relate to amendments of documents/information that are part of the clinical trial application dossier.

2) Submission of information is only obligatory if the amendment is a substantial amendment. Directive 2001/20/EC does not require notification, or immediate submission of information on non-substantial amendments. In other words, the

[8]Communication from the Commission - ('CT-1') (2010/C 82/01) https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52010XC0330(01)

[9]Detailed guidance from the Commission ('CT-2') (2006) https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/12_ec_guideline_20060216_en.pdf

only communication mechanism of substantial changes to information in the protocol or clinical trial dossier is through the submission of a substantial amendment. Non-substantial amendments, or changes that do not relate to information submitted in the clinical trial application dossier should be recorded in the documentation when it is subsequently submitted, for example in the subsequent submission of a substantial amendment (CT-1 section 3.1).

In case the risk assessment leads to actions that affect the trial as described below in a), b), and c), the relevant NCA and/or Ethics Committees must be informed in accordance with Directive 2001/20/EC and national laws:

a) It is possible that urgent actions are required by the sponsor and investigator to protect the trial participants against immediate hazard. These urgent safety measures do not need prior notification. Due to specific local or national circumstances related to the COVID-19 Pandemic, submission to the relevant authorities could take longer than usual, but the information needs to be provided to the NCA and the Ethics Committee as soon as possible (CT-1, Art 3.9). The sponsor needs to document the justification for this delay in the trial master file. In communication with authorities, the sponsor is expected to provide adequate information on the cause, measures taken and the plan for further actions.

b) If changes, which are substantial amendments, do not require immediate action from the sponsor or investigator, these should be submitted as substantial amendment applications. Sponsors are encouraged to take into account the limited capacity of regulatory authority assessors and Ethics Committees, and submit only high quality, complete applications containing only the necessary changes. Over-reporting should be avoided (Art. 11b of Directive 2001/20/EC; CT-1 article 3.9).

c) Certain procedural or other changes might become necessary to address global or local consequences of the pandemic (e.g. related to social distancing or to avoid unnecessary strain on health care professionals). If these changes are justifiable, COVID-19 related changes, not related to trial participants' safety and do not have a serious effect on the benefit-risk balance for the trial participants and the scientific value of the trial, they can be notified as soon as possible taking into account national and local circumstances. In these cases, sponsors are expected to submit to the relevant NCA and Ethics Committee the list of all changes with appropriate risk assessment and justification as well as follow-up actions when necessary. Cumulative changes must not have a negative impact on trial participants' safety and/or on the integrity of the trial. Relevant protocol deviations are sufficient to be recorded according to chapter 13.

The sponsor is expected to maintain appropriate records, in a timely manner, of all changes described in the chapter above in the trial master file.

Communication should be clearly marked with 'COVID-19' in the subject field.

The following table provides a non-exhaustive list of examples for the classification of different mitigating measures – more information on specific approaches can be found in the chapters 3, 9 and 11 below, and/or in the national recommendations, where applicable.

Urgent safety measures (a) (in light of the conditions described above)	Substantial amendments (b) (in light of the conditions described above)	Other measures (c) (in light of the conditions described above)
Temporary halt due to shortage of trial medication		Temporary halting of a trial, when it is not linked to the safety of trial participants
Direct distribution of IMP to trial participants/carer home or residence by a distributor in case of **exceptional emergency situations** (please refer to chapter 9 for more detail)	Direct distribution of IMP to trial participants/carer home or residence by a distributor (please refer to chapter 9)	
Testing is performed in local laboratories instead of at the trial site		
	Introducing remote SDV (in exceptional cases, see chapter 11)	
Transfer of trial participants to another trial site, but treatment is continued		
Temporary de-activation of the trial site with discontinuation of treatment		
	Changes to the as per protocol informed consent process	
Opening of new trial sites or relocation to existing trial sites to accommodate for the transfer of existing trial participants in case of emergency situations		
		Supplying trial participants with larger amounts of IMP under the supervision of the investigator

7. AGREEMENT WITH AND COMMUNICATION BETWEEN SPONSORS, TRIAL SITES AND TRIAL PARTICIPANTS

Changes to trial conduct initiated by the sponsor should be agreed with and communicated clearly to investigators. To support implementation by sites, it is important that changes and local implications are made clear, e.g. by marking changed documents with track changes or providing summary of changes. Agreements may be documented as e-mail exchange.

Vice versa, investigators may initiate changes to trial conduct as urgent safety measures. These should be reported as soon as possible by the investigator to the sponsor as well as

by the latter to the competent authorities and ethics committees, in line with the principles described in chapter 6.

In addition, trial participants should be informed by the investigator, in a timely manner, about changes in the conduct of the clinical trial relevant to them (e.g. cancellation of visits, change in laboratory testing, delivery of IMP).

8. CHANGES TO INFORMED CONSENT

Unless linked to the implementation of urgent safety measures, changes in informed consent procedures will need to be reviewed and approved by the relevant ethics committee in advance.

The informed consent procedure in all trials needs to remain compliant with the trial protocol as well as with EU and national legal framework. It is acknowledged that national provisions and approaches differ.

Sponsors should be mindful of the current pressure on the medical profession and should carefully assess the pertinence of enrolling new trial participants in ongoing clinical trials. Absolute priority should be given to clinical trials for the prevention or treatment of COVID-19 and COVID-19-related illnesses, or trials on serious diseases with no satisfactory treatment option. In case a sponsor plans to initiate a trial aiming to test new treatments for COVID-19, advice should be sought on alternative procedures to obtain informed consent, in case the physical consent cannot leave the isolation room, and therefore is not appropriate as trial documentation.

However, the following specific aspects should be taken into account with trials involving COVID-19 patients:

- If written consent by the trial participant is not possible (for example because of physical isolation due to COVID-19 infection), consent could be given orally by the trial participant (Art 2(j) of Directive 2001/20/EC) in the presence of an impartial witness. In such cases, the witness is required to sign and date the informed consent form and the investigator is expected to record how the impartial witness was selected.

- In addition, it could be considered that the trial participant and the person obtaining consent sign and date separate informed consent forms.

  In either case, all relevant records should be archived in the investigator's site master file. A correctly signed and dated informed consent form should be obtained from the trial participant later, as soon as possible.

- Where potential COVID-19 trial participants are incapacitated adults not able to give informed legal consent due to the severity of their medical condition, or when minors are included, consent has to be obtained from the legal representative(s) according to Articles 4 and 5 of Directive 2001/20/EC or according to national rules.

- In case of acute life-threatening situations, where it is not possible within the therapeutic window to obtain prior informed consent from the trial participant (or

her/his legal representatives(s)), informed consent will need to be acquired later, when this is allowed by national legislation. In these cases, the investigator is expected to record why it was not possible to obtain consent from the trial participant prior to enrolment.

There may be a need to re-consent already included trial participants. However, it should be avoided that trial participants visit trial sites for the sole purpose of obtaining re-consent. If re-consent is necessary for the implementation of **new urgent changes in trial conduct** (mainly expected for reasons related to COVID-19 or important safety issues for other trials), alternative ways of obtaining such re-consent should be considered during the pandemic. These could comprise contacting the trial participants via phone or video-calls and obtaining oral consents, to be documented in the trial participants' medical records, supplemented with e-mail confirmation. Approved updated patient information sheet and consent form should be provided to trial participants by the investigator by e-mail, mail or courier before re-consent is obtained. Any consent obtained this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity when the trial participants are back at the regular sites.

Any validated and secure electronic system already used in the trial in the particular member state for obtaining informed consent can be used as per usual practice and if in compliance with national legislation.

9. CHANGES IN THE DISTRIBUTION OF THE INVESTIGATIONAL MEDICINAL PRODUCTS

The recommendations in this section of the guidance also apply to "non-investigational medicinal products" (NIMP) and other products or devices normally provided to the trial participants during on-site trial visits, as defined in the protocol.

Changes in the distribution of the investigational medicinal products (IMP) may be necessary to prevent avoidable visits to sites and to provide the trial participants with needed treatments. Sponsors must assess the risks relating to the product and consider any alternative shipping and storage arrangements.

Such measures raise various practical considerations, including whether the IMP is appropriate for administration and general storage at the trial participant’s home, how the stability of the product will be maintained during transit (especially for a cold chain product), how safe custody of products will be ensured and how IMP accountability and the evaluation of compliance to treatment (as defined in the protocol) will be managed.

The overriding objective of all changes in distribution is to provide trial participants with the IMP as needed according to the trial protocol and to avoid treatment interruptions, in order to maintain a positive benefit-risk balance and to protect the rights, safety and well-being of trial participants as well as the integrity of the data collected during the clinical trial. The continuation of treatment should be under adequate supervision of the responsible investigator.

Changes in distribution of IMP may include the following:

- Provided that such measures do not create shortages of marketed medicinal products:

  - Larger amounts of IMP than normally foreseen can be provided to the trial participant. This is to sustain the trial participant for a longer period and thereby avoid non-critical visits by the trial participant to the investigator site.
  - It is recommended for all IMPs and non-IMPs in clinical trials that appropriate stock is maintained to ensure treatment in case of distribution failure.

- In case of urgent shortage of IMP at some sites or transfer of trial participants from one clinical trial site to another site, there might be a need to potentially re-distribute the IMP between sites in accordance with GMP annex 13 (section 47). This should only be considered in cases where a direct distribution of the IMP to a trial site by the usual distributor is not possible or in the exceptional circumstance where a trial participant is transferred from one site to another. Sponsors should assess whether sites can handle and control such a re-distribution process, especially in case of restricted conditions for storage such as the need for specific conditions other than room temperature (e.g. -20°C, +2-8°C).
- Re-distribution should follow a written procedure established in cooperation with the Qualified Person or the person responsible for distribution of the IMP, and sites should be provided with enough information to ensure that the process can be performed securely. Appropriate associated records should be included in the transfer and retained. Adequate documentation of the transfer needs to be included in the investigators' and the sponsor's trial master file.
- In line with the reduction of physical site visits, we foresee that there will be a need for delivery of the IMP directly to trial participants' homes during the COVID-19 pandemic to avoid that the trial participant has to reach the site with the consequent risk of spreading/acquiring infection. The following should be considered for the direct shipment of IMP to trial participants:

  - It should also be determined whether further education or training of the trial participants will be necessary for IMP receipt, handling and self-administration. Written information on the dose regimen needs to be provided to trial participants along with contact information to site for any questions they may have. The same contact should be used for trial participant to inform the investigator if there is any damage to the IMP packaging, containers or the IMP itself.

  - The delivery should be done from trial sites (hospital pharmacies as applicable) to trial participants. The sponsor should bear the cost of the shipment and should provide logistical assistance to the trial site if needed, for instance for the selection of an appropriate courier or transporter.

  - If, due to the COVID-19 pandemic, a trial site is not able to handle the additional burden of IMP shipment to trial participants, the IMP may as an exception be shipped to the trial participants by a distributor[10] independent from

[10]A distributor is a third party located in the EU/EEA contracted by the sponsor to store the IMP and distribute it to the trial sites and, in the current exceptional circumstances, to the home of the trial participant.

and acting on behalf of the sponsor in line with national law or temporary national emergency measures[11]. The following then applies:

- IMP shipment to the trial participants should be described in a contract between the sponsor and the distributor. The contract should identify all involved investigators/ trial sites. The contract should set out what documents or other materials are permitted to be supplied to the site. The contract and procedures involved should be documented in the sponsor trial master file.
- The IMP may only be dispatched to trial participants after agreement with the investigator and on the basis of the investigator's prescription. The agreement and the procedure should be recorded in the investigator site file;
- The investigator should explain the process to the trial participant or carer orally and should obtain her/his oral consent before agreeing with the sponsor, including for the investigator to provide the trial participant's name, address and contact details (phone and or e-mail) to the distributor. When possible, consent should be confirmed in writing by e-mail, mail or letter sent via a courier. The oral or written consent should be documented in the trial participant's medical records;
- The distributor should not store the personal data of the trial participant for a longer period than is required for the purpose of dispatching the IMP (should be destroyed as soon as no longer needed and in no case longer that the duration of the public health crisis) **and should only use this information for the purpose of making the IMP deliveries during the period of the pandemic**. It should not be used for any other purpose or disclosed to a third party for another purpose, other than monitors, auditors or inspectors verifying the conduct of the trial. This should be set out in the contract between the sponsor and distributor.
- The trial participants' names, address and contact details should never be provided to the sponsor, and the distributor should not have access to the trial participants' health information.

- The organisational measures agreed between the sponsor and the contracted distributor should protect blinding and ensure compliance with the randomisation.
- Dedicated couriers should be contracted for IMP shipment with procedures in place. These procedures should ensure timely delivery directly to the trial participant or her/his designated caregiver to avoid that e.g. the IMP is handed over to the neighbour etc. The investigator should receive confirmation of all deliveries by the courier and confirm the receipt with the trial participant/caregiver by e.g. phone-call or e-mail. The investigator is responsible for proper IMP administration.
- The shipment should be done under conditions that safeguard the integrity of the IMP, whether physically or with regards to temperature. Temperature

[11]The provision of IMP directly from an independent distributor to participants under specific conditions was shared with the health ministers and no concern was raised in the videoconference of Ministers of Health of 27 April 2020.

records should be maintained during shipment for temperature-sensitive products. The investigator should be immediately informed in case the temperature departs from the specified conditions and should advise the trial participant at the earliest on the possibility to use or not the IMP, after consultation with the sponsor.

- The courier should be informed of, and commit to, the shipment conditions (in particular regarding temperature) and maximum duration.
- Procedures for the accountability of the IMP must be in place (among others for compliance monitoring). Accountability of the IMP should be maintained. Clear records of shipment from the trial site or from the distributor should be kept in the investigator site file, itemising the medication being delivered and the quantity involved. Documentation of receipt by the trial participant should be kept. Participants should retain unused IMP and containers and return them to the investigator when they next have a visit to the investigator site

Changes in IMP distribution are often associated with additional changes (e.g. in the visits schedule per protocol or replacement of physical visits with virtual ones). Such changes need to be communicated to regulatory bodies as described in section 6.

10. CHANGES IN THE DISTRIBUTION OF *IN VITRO* DIAGNOSTIC AND MEDICAL DEVICES

It is important to ensure the availability of those *in vitro* diagnostic devices and medical devices, which are essential for the conduct of the clinical trial (e.g. to allow enrolment, monitoring trial participants' safety and treatment efficacy, providing data for trial endpoints). Therefore, it is recommended that appropriate stock of these devices is maintained in case of distribution failure, if this can be done without posing any risk to the treatment of patients outside of the clinical trial under standard medical care. In addition, changes in the distribution of these devices between trial sites may be necessary.

11. CHANGES TO MONITORING

Certain sponsor oversight responsibilities, such as monitoring and quality assurance activities need to be re-assessed and temporarily, alternative proportionate mechanisms of oversight may be required.

The first priority when considering any change is to protect the rights, safety and well-being of trial participants.

As part of the risk assessment outlined in chapter 5, a risk-based approach to monitoring should be taken, focusing on certain sites, certain data points and certain processes that are critical to ensure the rights, safety and well-being of trial participants and the integrity of the trial (and trial data). The sponsor should consider the extent and nature of monitoring that would be eligible in each specific trial under this **exceptional** situation, and weigh this against the extra burden that introduction of any alternative measures would put on site staff and facilities. The monitoring plan should then be revised in accordance with these considerations, in order to strike an acceptable balance between appropriate oversight and the capacity of the trial site.

Results of adjusted monitoring/review measures and their impact should be reported to the sponsor in monitoring reports and in the clinical study report, where applicable.

It is essential that robust follow-up measures are planned and ready to be implemented when the situation is normalised. This should include increased on-site monitoring for a period that is sufficient to ensure that the impact of the reduced monitoring can be rectified, and problems resolved or properly documented. Data subject to remote source data verification are likely to require re-monitoring, in particular if it was based on pseudonymised documents, which cannot be considered as source documents, and considering that remote monitoring is expected to only have focused on the most critical information.

Adjusting monitoring activities may include a combination of the following:

a) On-site monitoring

Cancelling or postponing of on-site monitoring visits and extending of the period between monitoring visits are likely to be necessary.

To the extent on-site monitoring remains feasible, it should take into account national, local and/or organisational social distancing restrictions, the urgency (e.g. source data verification can often be postponed) and the availability of site staff and should only be performed as agreed with trial sites.

Additional measures regarding on-site monitoring may include limited, targeted on-site monitoring identifying higher risk clinical sites, if not already applicable for the trials of concern.

The on-site monitoring plan will need to be adapted and alternative measures (like those outlined in b), c) and d) below) put in place, or relied on to a greater extent if already present.

b) Centralised monitoring and central review of data collected

Centralised monitoring is an established method under ICH GCP E6. 5.18.3 (Addendum). In the context of the pandemic, the role of centralised monitoring has an increasing importance. Centralised monitoring of data acquired by electronic data capture systems (e.g. eCRFs, central laboratory or ECG / imaging data, ePROs etc.) that are in place or could be put in place provides additional monitoring capabilities that can supplement and temporarily replace on-site monitoring through a remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner. Centralised monitoring should not be confused with remote source data verification (see 11.d. below).

c) Off-site monitoring

Additional off-site monitoring activities could include phone calls, video visits, e-mails or other online tools in order to discuss the trial with the investigator and site staff. These activities could be used to get information on the clinical trial progress, to exchange information on the resolution of problems, review of procedures, trial participant status as well as to facilitate remote site selection and investigator training for critical trials.

d) Remote source data verification

In addition to the above mentioned, established methods (11.a-c), and taking into account the continuing nature of the COVID-19 pandemic and the need to ensure the quality of

clinical trial data and to protect the rights, safety and well-being of the participants in the EU/EEA, remote source data verification (rSDV) can be justified in clinical trials. Remote SDV can be considered only during the COVID-19 pandemic related public health crisis and when in line with EU and national law (or temporary national emergency measures)[12]. Remote SDV may be considered for trials:

- involving COVID-19 treatment or prevention;
- investigating serious or life-threatening conditions;
- where the absence of SDV for critical data may likely pose unacceptable risks to participants' safety or the reliability/integrity of trial results;
- involving particularly vulnerable participants such as children or those temporarily (e.g. trials in emergency situations) or permanently (e.g. trials in patients with advanced dementia) incapable of giving their informed consent or
- in pivotal trials.

Remote SDV should focus on the quality control of critical data such as primary efficacy data, important safety data. Important secondary efficacy data may be monitored simultaneously, provided this does not result in a need to access additional documents and therefore in an increased burden for trial site staff. The sponsor should determine the extent and nature of remote SDV that they consider needed for each trial under this exceptional situation and should carefully weigh it against the extra burden that introduction of any alternative measures would put on site staff and facilities.

In the case of these trials, principal investigators should make their own determination as to whether or not the situation at their clinical site allows any of the following options for remote SDV:

- Sharing pseudonymised copies of trial related source documents with the monitor; this may be done electronically where manageable by the site staff;
- Direct, suitably controlled remote access to trial participants' electronic medical records;
- Video review of medical records with clinical site team support, without sending any copy to the monitor and without the monitor recording images during the review.

For COVID-19 trials starting now, when remote SDV is foreseen, it should be described in the initial protocol application (and informed consent form). In case of ongoing trials introduction of remote source data verification should be submitted, in line with national law or temporary national emergency measures, via a substantial amendment. These provisions should be in line with the principles of necessity and proportionality and in a way that protects trial participants' rights and should not place any disproportionate burden on site staff as determined by the investigator and trial site staff.

Remote SDV can be carried out only in agreement with the investigators who should not be put under undue pressure to accept remote SDV and should always give priority to the care to be given to trial participants and other patients.

[12] The initial provision for source data verification to take place remotely in the case of trials with (1) COVID-19 treatments and (2) medicines for treatment of serious or life-threatening conditions with no satisfactory treatment option, provided that certain conditions are met to protect trial participants' rights was shared with the health ministers and no concern was raised in the videoconference of Ministers of Health of 27 April 2020. The scope for rSDV was further extended in February, 2021 (v4) due to the prolonged nature of the pandemic.

Remote SDV should not be carried out if adequate data protection, including data security and protection of personal data even if pseudonymised, is not ensured. Refer to Annex 1 for controls that, where applicable, can protect trial participants' rights while permitting remote SDV.

12. CHANGES TO AUDITING

In the current situation, on-site audits should, in general, be avoided or postponed. Audits should only be conducted if permitted under national, local and/or organisational social distancing restrictions. For critical trials, on-site audits as well as remote audits can be considered, after agreement with the investigator and if the audits are assessed as essential, e.g. triggered audits with the purpose of investigating serious deviations from the trial protocol or from the applicable legislation.

13. PROTOCOL DEVIATIONS

The COVID-19 situation is likely to introduce more protocol deviations than normal. It is expected that the sponsor manages such protocol deviations in accordance with their standard procedures. The sponsor should perform an analysis of the number and type of deviations periodically to assess whether a protocol amendment or other modifications are needed. A proportionate approach will be taken by the GCP inspectors when such deviations are reviewed, recognising that the best interest of the trial participants is maintained, and the trial participants are not put at risk.

An increase in protocol deviations in relation to the COVID-19 situation will not, of itself, trigger the actions required by ICH GCP section 5.20. Such deviations will need to be assessed and reported in the clinical study report, following ICH E3.

Please also refer to the guidance on the implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials[5] by the CHMP Biostatistics Working Party, published on 25 March 2020.

14. REIMBURSEMENT OF EXCEPTIONAL EXPENSES

Taking into account this exceptional situation, the implementation of urgent safety measures may create unplanned expenses. These expenses should be borne by the sponsor, preferably directly. If expenses nevertheless arise which have to be borne initially by the trial participants, these should typically be compensated subsequently by the sponsor via the investigator. If additional financial compensation is provided to sites/investigators (e.g. to cover the cost of using couriers for IMP delivery), this needs to be documented and performed according to national legislation. Handling of reimbursement of such expenses should follow national legislation and/or guidance.

15. INITIATION OF NEW TRIALS AIMING TO TEST NEW TREATMENTS FOR COVID-19

The Member States support the submission of large, multinational trial protocols for the investigation of new treatments for COVID-19[13].

[13]https://www.ema.europa.eu/en/news/call-pool-research-resources-large-multi-centre-multi-arm-clinical-trials-generate-sound-evidence

Sponsors are encouraged to submit such applications for assessment via an accelerated Voluntary Harmonisation Procedure[14] (VHP) when possible. In order for harmonised review times to be minimised, sponsors should contact the proposed Reference NCA, in advance, to explore the feasibility of an accelerated VHP (plus) process.

The developers of medicines or vaccines are invited to contact EMA as soon as possible using the e-mail address [redacted]. EMA provides a full fee waiver and a fast-track procedure for scientific advice[15].

[14]Please note that enclosed procedure is applicable for routine assessments, accelarated assessment of COVID-19 trial applications is foreseen; https://www hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2016_06_CTFG_VHP_guidance_for_sponsor_v4.pdf

[15]https://www.ema.europa.eu/en/news/covid-19-developers-medicines-vaccines-benefit-free-scientific-advice

Annex 1: Protection of trial participants' rights during remote source data verification

The implementation of the following controls can help to appropriately protect trial participants' rights while permitting remote source data verification (SDV). Remote SDV should follow the principles laid out it Section 11.d.

- The principal investigator (PI)/PI's institution and the sponsor may be jointly responsible as controllers for ensuring information is safeguarded[16]. Remote SDV of medical records of EU/EEA trial participants may generally take place from a (remote) monitoring location within EU/EEA. In case the data are transferred/processed outside the EU/EEA, one of the transfer tools under the General Data Protection Regulation (GDPR)[17] needs to be in place; in practice, unless an adequacy decision adopted by the European Commission applies, it should be contractually ensured that a level of data protection essentially equivalent to Union data protection legislation will be applied.

- A documented risk assessment should be performed to establish the risk to the trial participants and to the trial if SDV cannot be performed in the near future. **Critical data for which SDV needs to be performed should be identified by the sponsor in a monitoring plan and should be focused on primary efficacy data and important secondary efficacy data if they are documented on the same source document and important safety data.** It is important to ensure that only the data that is necessary for this purpose is accessed.

- The sponsor should consult with their data protection officer (DPO) and with the PI at each site to establish whether remote SDV would be allowed, feasible and manageable for this site and what the practicalities could be.

- If the PI/PI's institution, in consultation with their DPO, confirms their agreement to the conduct of remote SDV in writing, a substantial amendment should be submitted to the Ethics Committee and/or NCA where required before proceeding, with a justification of the urgency of the remote SDV and their risk assessment.

- Site staff and monitors should be trained on the remote SDV process.

- Site staff should inform each trial participant or designated legal representative and ensure that they do not object to the remote review of their records for trial purposes and document this process in the trial participant's medical records.If a trial participant objects to remote review of their records, no remote SDV will occur for that trial participant.

- Performance of remote SDV by the monitor may only occur in locations that prevent viewing by any unauthorised person, through a secure internet connection and on a computer appropriately protected against unauthorised access to the data.

[16] See also European Data Protection Board Guidelines 07/2020 on the concepts of controller and processor in the GDPR – version for public consultation, p. 21-22.

[17] Regulation (EU) 2016/679, OJ L 119 4.5.2016, p. 1

- Monitors should sign a written confidentiality agreement committing to securely destroy any copy of redacted documents, whether paper or electronic, as soon as they have been used for source data verification and committing not to make any copy (or recording in the case of video access) of any non-pseudonymised document.

- If the agreed remote SDV process involves redaction by the site staff (pseudonymisation) of source records:
    - The monitor should provide a written request to the site for the specific participant's specific trial records required for SDV.
    - Site staff should create copies of the requested trial participant's records, redact (i.e. pseudonymise and mask any unnecessary private information unrelated to the trial) the copies, identify them with the trial participant identification code in the trial, have a second person perform and document a quality control to ensure that all identifying information has been redacted and is no longer readable, and make the pseudonymised copies available to the monitor using a secure mechanism. The redacted copies should be kept in the investigator's site master file with records of their communication to the monitor.
    - The monitor should access the records securely, complete the monitoring task, securely destroy any copy made locally and provide a certificate of destruction to the trial site.
    - Once on-site monitoring visits are again feasible, the monitor should verify at the earliest opportunity that the provided pseudonymised (coded) data are indeed data related to the trial participant with the provided code.

- If the agreed remote SDV process involves a video review of records:
    - The quality of the video should be adequate to enable reading, without risk of confusion between similar characters, and to avoid a negative impact on the visual health of the monitors.
    - The video review of documents may include site staff sharing the screen of their computer with the monitor using a secure video conference application hosted on their computer. Videoconferencing solutions where data may be captured on third country servers may not be acceptable.
    - The video review of documents is likely to necessitate the presence of a member of the trial site staff at all times in order to change the document being viewed or to scroll the document on a computer screen. Sponsors and investigators should be aware of the importance of the burden that such SDV methods may represent for trial sites and hence the review should be restricted to a minimum of critical data in critical trials.
    - The transmission of the data should be adequately protected against unauthorised third party access.

- If the agreed remote SDV process involves the site providing the monitor remote access to the site electronic medical record (EMR) system:
    - The monitor should be provided with a secure, read-only access to the EMR system, including all modules relevant for review. This access should be restricted to the records of only those patients who participate in the trial and who did not object against remote access to their medical records as outlined above.

  - A list of the monitors to whom remote access has been granted should be maintained. In order to prevent unauthorised access, access rights should be revoked once remote SDV tasks have been completed for the trial.
  - The EMR system should have an audit trail and be able to log information on who accessed data and when.
  - Remote access to the EMR should only be possible using a two-factor authentication.

- It should not be possible to make local copies of trial participants' health records. Users should be aware of the automatic creation of temporary files on their computer when reviewing trial participant data, and should securely delete such files immediately after each source data verification session.

Supplementary recommendations of BfArM and PEI to the European Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, version 4

In view of the impact of the pandemic on European healthcare systems, the European authorities published a guidance document on 20 March 2020 that provides sponsors with recommendations regarding clinical trials and the persons involved in them.

This guidance document was revised again, adopted on 4 February 2021 and published as version 4 both in the collection of laws of the European Commission (Eudralex, Volume 10)[1] and on the homepage of the European Medicines Agency (EMA)[2].

The guideline is a harmonised package of recommendations at EU level, which was co-developed and co-adopted by Germany. Some recommendations require closer consideration and interpretation, also with regard to the German legal area. These include, in particular, temporarily applicable measures for source data verification, if on-site monitoring at the trial sites is not indicated due to the coronavirus pandemic.

Additional notes and recommendations for the implementation of Remote Source Data Verification (rSDV)

This document does not repeat the recommendations of the European guideline in a comprehensive manner. Instead, only those recommendations that require interpretation and supplementation or for which the sponsor is expected to provide detailed information in an initial application in accordance with § 7ff GCP-V (Ordinance on the implementation of GCP in the conduct of clinical trials on medicinal products for use in humans) or an application for a subsequent amendment in accordance with § 10 GCP-V ('substantial amendment'), which prove that the planned procedure corresponds to the state of science and technology, are taken up in the following.

Regardless of the method chosen for rSDV, the sponsor shall first obtain the written agreement of the investigator and, if applicable, of the institution where the trial site is located.

As described in detail in the European guideline, remote access to source documents/source data for monitoring purposes should only take place **in justified exceptional cases** and **only to the extent strictly necessary**. For details, see the European guideline. Remote SDV should also only take place if suitable data protection - including data security and the protection of personal data – is ensured. This is also to be borne in mind with regard to pseudonymised data.

In justified exceptional cases, the guideline provides the following three options for source data reconciliation without the monitor being physically present at the trial site:

- The trial site provides the monitor, under the responsibility of the investigator, with copies of the source documents/source data in which personal identifying information of the trial subjects and information pertaining to their privacy has been obscured or redacted (hereinafter referred to simply as "redacted copies").
- Under the responsibility of the investigator, the trial site grants the monitor direct, controlled remote access to the systems with which the source documents/source data are managed.

[1] https://ec.europa.eu/health/documents/eudralex/vol-10_en

[2] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/goodclinical-practice#guidance-on-clinical-trial-management-during-the-covid-19-pandemic-section

- The trial site grants the monitor, under the responsibility of the investigator, passive access to the source documents/source data via live image transmission (e.g. sharing of the screen or image/sound transmission).

Implementation requires the authorisation of the responsible higher federal authority as well as the favourable opinion of the responsible ethics committee. For this purpose, an application according to § 7ff GCP-V or for subsequent amendment according to § 10 GCP-V ('substantial amendment') shall be submitted. In this application, the planned procedure should be described in sufficient detail, beginning with a summary of the underlying, study specific risk assessment. This can be done either in the Quality Control and Quality Assurance section of the protocol (ICH-GCP, Section 6) or as an appendix to the protocol. In the latter case, the appendix to the trial protocol must be submitted with the application.

Irrespective of this, the standard operating procedures and study specific documents (including those on risk-based quality management [ICH-GCP, Section 5.0] and monitoring [ICH-GCP, Section 5.18]) used in the clinical trial should be adapted accordingly.

The method chosen for the rSDV depends very much on the infrastructure of the trial site. In the application for approval according to § 7ff or § 10 GCP-V, the sponsor shall list **all** methods that may be used for rSDV, as only the alternatives described therein are considered approved.

For each method applied for, at least the following information should be provided:

- Identification of the source documents/source data to be made available under the rSDV (e.g. those related to the primary endpoint, serious adverse events, important medical events, or the reasons for exclusion of a subject from the trial);
- Presentation of the precautions taken for data security to ensure the confidentiality of data and the privacy of the trial subjects.

Depending on the method applied for, the following additional information is required:

a. Passing on of redacted copies of original documents and documents with original data

The sponsor shall provide the following details in the protocol or in an annex to the protocol:

- Minimum copy quality requirements to be met by investigator/institution (e.g. format, resolution, colour);
- Method for ensuring that the copies are complete;
- Method for ensuring that all information that could reveal the identity of subjects is obscured or redacted, and a description of actions to be taken by the monitor and the investigator/institution if this has failed;
- Requirements to prevent loss of or unauthorized access to source documents/data during the document/data sharing process;
- Documentation requirements for the traceability of documents forwarded by the investigator/institution as well as received and processed by the monitor.

b. Direct, controlled remote access to the systems used by the trial site to manage the source documents/source data

The sponsor shall clarify the following in the application for approval:

- Name of the document management system(s) to be accessed (name of the software, version);
- Name of the system used for remote access (name of the software, version, end-to-end encryption requirement);
- Monitor access rights (two-factor identification, access limited to the trial subjects and the parts of the documentation provided for under the rSDV, right to navigate, read-only access);
- Measures to prevent permanent storage of file contents by the monitor or to ensure short term, permanent deletion of automatically generated, temporary contents;

The sponsor shall provide a written statement in the application for approval:

- Confirmation that the rSDV is conducted exclusively by the authorized person(s) (i.e. monitor) in accordance with the written informed consent of the trial subjects.
- Confirmation that remote access is provided via secured systems/environments and systems/servers within the EEA/EU and/or confirmation that the conditions set out in the European guideline for data transferred or processed outside the EEA/EU, are applied.

Note:

When establishing remote access or adding such access to an existing system, it should be ensured that the establishment or modification of such an access is validated according to the risk. Changes in running systems without sufficient validation (e.g. *quick-fix engineering updates* (QFE)) should be avoided.

c. Passive access to original documents/original data via live image transmission

The sponsor shall clarify the following in the application for approval:

- Brief description of the method used and the parties involved in the process;
- Identification of the devices and/or software used for live image transmission;
- Security measures applied (e.g. for authentication, prevention of unauthorised recordings or transmission security).

The sponsor shall make a written statement in the application for approval:

- Confirmation that the rSDV will be conducted exclusively by the authorised person(s) (i.e. monitor(s)) in accordance with the written informed consent of the trial subjects;
- Confirmation that live image transmission takes place via secured systems/environments and systems/servers within the EEA/EU and/or confirmation that the conditions set out in the European guideline for data transferred or processed outside the EEA/EU, are applied;
- Confirmation that there is a written statement from the monitor and the sponsor that
  a) the rSDV takes place in a protected environment (i.e. providing protection from unauthorised access in any form, including the use of privacy screens to prevent unauthorised viewing of source documents/source data);
  b) the viewed source documents/source data are not permanently stored and
  c) if necessary, temporarily saved files (including ones automatically generated by the system) are permanently deleted at short notice;

- Confirmation that appropriate corrective measures will be implemented in the event of technical difficulties or if the security of the transmission is no longer guaranteed.

Note:
The information and communication technology used by the sponsor and the trial site for rSDV shall be designed in such a way that secure and GDPR-compliant transmission is guaranteed. As a rule, the known messenger services are not suitable for this purpose. In this context, we refer to the "Whitepaper Technical Data Protection Requirements for Messenger Services in the Hospital Sector" published by the Conference of Independent Data Protection Supervisors of the Federal and State Governments on November 7, 2019[3].

Service providers for telemedicine who have the certificates, expert opinions and quality seals required according to § 5 para. 2 of Annex 31b to the Federal Master Treaty for Medical Practitioners [4] could be suitable for this purpose, provided that GCP-relevant aspects are guaranteed by the sponsor through the qualification and monitoring of these service providers.

In accordance with their legal mandate, the ethics committee and the responsible competent higher federal authority examine the information provided in the context of the evaluation or approval of an application, respectively, in accordance with § 7ff or § 10 GCP-V only cursory in relation to compliance with data protection regulations (see also “Coming into effect of the GDPR — Handbook for Ethics Committees for the Consultation or Evaluation of Studies”). The activities undertaken should be included by all parties involved in rSDV in their list of data-processing activities, which is anchored in data protection law, and might be subject to an independent assessment by the responsible data protection supervisory authorities.[5]

[3] https://www.datenschutzkonferenz-online.de/media/oh/20191106_whitepaper_messenger_krankenhaus_dsk.pdf

[4] https://www.gkv-spitzenverband.de/krankenversicherung/digitalisierung_und_innovation/ videosprechstunde/kv_videosprechstunde.jsp

[5] https://www.ak-med-ethik-komm.de/docs/intern-2018/DSGVO_Empfehlungen.pdf

10.10 Appendix 10: List of Abbreviations and Terms

Abbreviation/Term	Definition
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
anti-HBc	hepatitis B antibody
anti-HCV	hepatitis C antibody
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration time curve
AUC_{ss}	area under the concentration time curve at steady state
AZA	5-azacytidine
BID	twice a day
C1D1	Cycle 1 Day 1
CBC	complete blood count
CBF	*core binding factor*
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximal plasma concentration
COVID-19	coronavirus disease 2019
CR	complete response
CRh	complete response with hematologic improvement
CRi	complete response with incomplete blood count recovery
CT	computed tomography
CYP	cytochrome P450
DAC	5-aza-2-deoxycytidine
DMC	Data Monitoring Committee
ECG	electrocardiogram

Abbreviation/Term	Definition
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EFS	Event free survival
ELN	The European Leukemia Network
ENTO	entospletinib
EORTC-QLQ 30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D-5L	European Quality of Life 5 Dimensions Questionnaire
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
FLT3	FMS-like tyrosine kinase 3
GCP	Good Clinical Practice
GO	gemtuzumab-ozogamycin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HMA	hypomethylating agents
HOX49	homeobox protein
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ITD	internal tandem duplication
ITF	induction treatment failure
IV	intravenous
IWG	International Working Group

Abbreviation/Term	Definition
IxRS	Interactive Voice/Web Response System
MDS	myelodysplastic syndromes
MRD	measurable residual disease
mRNA	messenger RNA
MUGA	Multi-gated acquisition
N/A	Not applicable
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCCN	National Comprehensive Cancer Network
NPM1	*nucleophosmin-1*
NPM1-m	*nucleophosmin-1 mutated*
OS	overall survival
PK	pharmacokinetic(s)
PR	partial response
PD	progressive disease
pSYK	phosphorylated spleen tyrosine kinase
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS CoV-2	severe acute respiratory syndrome (SARS) coronavirus 2 (CoV-2)
SD	stable disease
SUSAR	suspected, unexpected serious adverse reaction
SYK	spleen tyrosine kinase
TEAE	treatment-emergent adverse event
TKD	tyrosine kinase domain
UGT1A1	UDP-glucuronosyltransferase 1A1
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization

Abbreviation/Term	Definition
WOCBP	woman of child-bearing potential

11.0 References

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