Janssen Research & Development *

Clinical Protocol

Phase 1-2 Safety and Efficacy Study of DACOGEN in Sequential Administration With Cytarabine in Children With Relapsed or Refractory Acute Myeloid Leukemia

Protocol DACOGENAML2004; Phase 1-2
AMENDMENT INT-2

JNJ-30979754 (decitabine)

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	11 Apr 2013
Amendment INT-1	18 Jun 2014
Amendment INT-2	06 Oct 2015

Amendments below are listed beginning with the most recent amendment.

Amendment INT-2 (06 Oct 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment was to correct errors noted in the selection criteria and typographical errors.

Applicable Section(s)	Description of Change(s)
Rationale: The inclusion/exclusion criteria were modified based on incorrect interpretation of selection criteria.	
Section 4.1, Inclusion Criteria #6	#6.2: Unit for serum creatinine; listed as dg/dL but should be mg/dL in the sentence below: Glomerular Filtration Rate (ml/min/1.73 m^2 = k*Height(cm)/serum creatinine (mg/dL) where k is a proportionality constant which….
Section 9.1.2 Screening Phase	#6.2: "and" changed to "or" in the sentence below: Cardiac function must be normal, defined as shortening fraction of ≥29% by echocardiogram, or left ventricular ejection fraction (LVEF) >58%. One of the 2 cardiac function parameters should meet the threshold as stated in footnote j in the Time and Events (T&E) Schedule.
Section 4.2 Exclusion Criteria	#5.1: Unit for white blood cell count listed as 40,000 cells/mL is incorrect and should be expressed in standard units resulting in 40 $x10^9$ cells/L
Rationale: To provide further clarification throughout the protocol, the timing of Day 28 assessments, the End of Sequential Treatment Visits, sample collection of cerebrospinal fluid, hematology testing was clarified, and the screening period in Figure 3 was corrected.	
T&E Schedule, column title	Clarified that the Day 28 assessments (end of cycle) can be later than Day 28, but have to occur within 8 days prior to the start of the next cycle.
T&E Schedule footnote b	Clarified that the End of Sequential Treatment Visit can occur within 7 days after the end of the last sequential treatment cycle.
T&E Schedule footnote r	Clarified the exception at screening for cerebrospinal fluid (CSF) collection: Samples will be collected from Phase 1 and Phase 2 subjects. 0.5 ml of CSF will be collected for PK analysis when/if CSF is obtained as part of routine medical care except at screening.
Section 9.2.1	Clarified that the hematology testing can be performed after Day 28 if the next cycle is delayed: Hematology including peripheral blast counts will be performed during screening, at Day 1, Day 5 (first cycle only), Day 8, Day 22 (first cycle only), and Day 28 or later if the next cycle is delayed but within 8 days of the start of the next cycle.
Figure 3	The scheme box for screening period was corrected, stating "Up to Day -14", instead of Day -10, for consistency with other sections.
Rationale: To align with the current protocol template or to provide further clarification within the protocol, minor updates were implemented as described below.	
Title page	Updated sponsorship statement on the title page to replace "Janssen R&D Ireland" with

Applicable Section(s)	Description of Change(s)
	"Janssen Sciences Ireland UC.
4.1 Inclusion Criteria; 4.2 Exclusion Criteria	Provided further granularity in describing the changes that were made for Amendment INT-1 versus the current Amendment INT-2.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-1 (18 June 2014)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to facilitate enrollment into the study and provide clarity on some aspects of the protocol.

Applicable Section(s)	Description of Change(s)
Rationale: The inclusion/exclusion criteria were modified based on feedback from investigators and to facilitate enrollment.	
Section 4.1	#3: Provisions were added to allow subjects who relapse following bone marrow transplant to enter the study. #6: The age range for adolescent children was specified (12 to 18 years of age). Requirements for contact with the sponsor's medical monitor were added in the event of elevated alanine aminotransferase (ALT) related to intrathecal treatment. Changed ALT upper boundary to ≤5 x upper limit of normal. #9 and #10: Criteria were modified to delete all references to donation of eggs or sperm because the patient population would not be allowed to donate based on age, medical history, and prior treatments.
Section 4.2, Synopsis	#3: Criterion has been modified to exclude subjects with central nervous system disease category 3 (CNS3), including its specifications. #8: Clarified to exclude subjects currently receiving treatment in an interventional investigational study.
Rationale: Clarifications were made to the timing of the Screening Period and the required procedures.	
Synopsis; T&E Schedule; Section 4; Section 9.1.2	Changed the Screening Period from Day -10 to Day -14 through Day 0.
T&E Schedule	Clarified that the Informed Consent form must be signed prior to the commencement of any screening procedures, but is not considered a screening procedure itself.
Rationale: To clarify cardiac assessment requirements	
T&E Schedule, footnote "j"	Added text: Results of cardiac assessments performed more than 14 days prior to enrollment are acceptable provided no potentially cardiotoxic medications were administered between that evaluation and Cycle 1 Day 1.
Section 4.1 #6; Section 9.1.2	Clarification of acceptable time interval for cardiac function tests prior to the study for screening.
Rationale: Investigational sites are being referred to the Investigational Product instruction manual for handling and preparation instructions for DACOGEN. This reference is now routinely included in protocols.	

Applicable Section(s)	Description of Change(s)
Section 6.1.1; Section 14.4	The handling and preparation specifications for DACOGEN were removed. A reference was added to the Investigational Product instruction manual (or equivalent) for these specifications.
Rationale: Removed cytarabine based on the fact that all health authorities have accepted cytarabine as non-investigational medicinal product (IMP)	
Section 6.1.2; Section 6.2	References to the Sponsor's responsibility for supply of cytarabine study drug were removed.
Rationale: For very small children, dose adjustments based on weight are performed standardly at all investigational sites, therefore it is being specified in the protocol to ensure consistency in dosing for all study sites and ensure accurate dosing for very small children.	
Section 6.3	For subjects <1 year old or subjects <10 kg, dosing of study drug should be based on the subject's body weight rather than body surface area (BSA). This conversion is calculated as dose described by BSA in mg/m^2 divided by 30 and multiplied by body weight (kg). A "Dose Delays" section was given a separate subheading of Section 6.3.1.
Rationale: Clarification in prestudy and concomitant therapy was made in response to questions from sites.	
Section 8	Wording for prestudy therapy was clarified. A separate paragraph was added allowing prophylactic intrathecal therapy and hydroxyurea until 1 day prior to Cycle 1 Day 1.
Rationale: To remove redundancy in the Overview of Study Procedures	
Section 9.1.1	Paragraph on blood sampling for biomarkers and pharmacokinetics assessments was removed.
Rationale: To clarify length of follow-up for assessment of long-term toxicity.	
T&E schedule, footnote "d"; Section 3.1.4	Follow-up is to include recording of any late-occurring, potentially study drug-related adverse events, date(s) of any further treatment, drugs, and doses used and date of death, and should occur every 3 months for a maximum of 3 years after the last subject is enrolled or until 80% of patients are deceased, whichever occurs first.
Rationale: Clarify the start of next cycle in response to questions from sites	
Section 9.1.3	The next cycle of study drug can be started per investigator decision if the subject has recovered from acute toxicity and does not meet any of the discontinuation criteria
Rationale: Clarify the tests required for bone marrow examination	
Section 9.2.1	Clarified testing required with added text as follows: "Cytogenetic evaluations will be performed at screening. If tests such as immunophenotyping and/or cytochemical evaluations have been done for standard medical care prior or within screening period, the data will be collected in the eCRF."
Rationale: To ensure compliance with protocol-specified pharmacokinetics evaluations treating (very) small children and lessen the burden for them	
Section 9.2.3; T&E Schedule, footnote "r"	Pharmacokinetics (PK) samples can be taken via a central line if the decitabine infusion is given peripherally. If attempts to place a peripheral line are unsuccessful, and decitabine is given through a single lumen central line, consider to only collect pre-infusion and post-infusion PK samples.
Rationale: To clarify frequency of urine pregnancy testing for female subjects.	
Section 9.5	Urine or serum pregnancy testing for females of childbearing potential at screening is required and during the study when clinically indicated
Rationale: Correction of minor errors; minor wording clarifications	

Applicable Section(s)	Description of Change(s)
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. Additions were made to the Abbreviations list as needed. Minor wording clarifications were made throughout.

SYNOPSIS

Phase 1-2 Safety and Efficacy Study of DACOGEN in Sequential Administration With Cytarabine in Children With Relapsed or Refractory Acute Myeloid Leukemia

DACOGEN®, the formulated product of the active agent decitabine (5-aza-2'-deoxycytidine), is a DNA hypomethylating agent approved for the treatment of older patients with acute myeloid leukemia (AML). This protocol extends the evaluation of DACOGEN to the treatment of relapsed/ refractory pediatric patients with AML from 1 month to less than 18 years old. This is an open label, multicenter Phase 1-2 study that investigates the pharmacokinetics (PK), safety, and efficacy of a sequential administration of DACOGEN followed by cytarabine.

OBJECTIVES AND HYPOTHESES

Primary Objectives

The primary objectives of the Phase 1 portion of Study DACOGENAML2004 are:

- to determine the maximum tolerable dose (MTD) of cytarabine (up to 2 g/m^2 per day x 5) that can be administered on Days 8-12 following treatment with DACOGEN 20 mg/m^2 per day on Days 1-5 of a 28-day cycle.
- to determine decitabine PK parameters from blood sampling on Day 5 of Cycle 1. (PK parameter determinations are a secondary endpoint in the Phase 2 portion of the study)

The primary objective of the Phase 2 portion of Study DACOGENAML2004 is to determine the response rate (complete remission [CR] + complete remission with incomplete blood count recovery [CRi]) in children with relapsed or refractory AML when treated with DACOGEN 20 mg/m^2 per day on Days 1-5 followed by cytarabine at the determined MTD on Days 8-12 for up to 4 cycles of treatment.

Secondary Objectives

The secondary objectives are to evaluate the safety profile of DACOGEN 20 mg/m^2 per day administered on Days 1-5 followed by cytarabine Days 8-12 for up to 4 cycles of therapy, to describe the duration of CR + CRi, and evaluate the overall response rate (CR + CRi + partial response [PR]) to treatment.

Other objectives are: to determine the event-free survival (EFS) and overall survival (OS) for subjects treated with the sequential administration of DACOGEN and cytarabine, to explore the pharmacodynamic effects of DACOGEN with respect to DNA hypomethylation status and gene expression, and to explore predictive biomarkers for response to DACOGEN and cytarabine sequential treatment. The plasma PK profile of decitabine is a secondary endpoint in the Phase 2 portion of this study. Additionally, levels of decitabine in the cerebrospinal fluid (CSF) will be evaluated if samples are collected as part of other required medical care.

Hypotheses

The hypothesis to be tested in the Phase 1 portion of this study is that DACOGEN administered at 20 mg/m^2 per day for 5 consecutive days followed by at least 1 g/m^2 per day (but not more than 2 g/m^2 per day) of cytarabine on Days 8-12 can safely be given to children with relapsed or refractory AML.

The Phase 2 portion of the study is based on the hypothesis that the sequential administration of DACOGEN and cytarabine induces responses in pediatric patients with relapsed/refractory AML. It does not have formal hypothesis testing but is aimed to obtain initial efficacy and additional safety data of the sequential administration of DACOGEN and cytarabine.

OVERVIEW OF STUDY DESIGN

For the Phase 1 portion of the study, a "rolling 6" design[39] is used. The total number of participants is dependent upon the number of cytarabine dose levels tested; the maximum number of which is 3 dose levels (1 g/m^2, 2 g/m^2, and 1.5 g/m^2) with a maximum of 18 evaluable subjects.

The Phase 2 portion of the study will be an open-label, single arm study of the sequential administration of DACOGEN and cytarabine in at least 15 evaluable children with relapsed or refractory AML. The primary endpoint for the Phase 2 portion is the CR + CRi response rate. The observed response rate of CR + CRi will be descriptively evaluated compared with a clinically uninteresting level of 20% and a clinically interesting level of 35%.

After completing up to 4 cycles of sequential DACOGEN - cytarabine treatment in either Phase 1 or Phase 2 of this study, subjects who, in the opinion of the treating physician, may benefit, can receive single agent DACOGEN at 20 mg/m^2 IV infusion over 1 hour on Days 1-5 every 28 days in the study Continuation Phase. Cycles can be repeated for as long as such treatment is considered beneficial. Subjects who discontinue DACOGEN - cytarabine sequential treatment may enter the Continuation Phase of the study if, in the opinion of the treating physician, the subject would benefit.

SUBJECT POPULATION

This study will enroll children with relapsed or refractory AML who are 1 month of age to less than 18 years old. Screening for eligible subjects will be performed within 14 days before administration of any study drug.

Major inclusion criteria are:

- Subject must have a histological diagnosis of AML according to the World Health Organization (WHO) classification
- Subject must have AML which has relapsed or is refractory to standard of care and for which no curative therapy exists
- Subject must have a Karnofsky or Lansky score of at least 50
- Subject must be recovered from acute toxicity of any prior treatment
- Subject must have adequate organ function

Major exclusion criteria are:

- Subject has had prior treatment with DACOGEN or azacitidine (Vidaza)
- Subject has acute promyelocytic leukemia (M3 subtype in the French-American-British [FAB] classification system).
- Subject has central nervous system disease category 3 (CNS3)
- Subject has AML associated with congenital syndromes such as Down syndrome, Fanconi anemia, Bloom syndrome, Kostmann syndrome or Diamond-Blackfan anemia, or bone marrow failure associated with inherited syndromes
- Subject is currently enrolled in the treatment phase of an interventional investigational study.

DOSAGE AND ADMINISTRATION

DACOGEN will be administered as a 1-hour IV infusion of 20 mg/m^2 once daily for 5 consecutive days on Days 1 to 5 of each 28 day cycle. Cytarabine will be administered as an IV infusion over 4 hours daily for 5 consecutive days (Day 8 to Day 12).

The MTD of cytarabine will be determined in the Phase 1 portion of the study. The starting dose of cytarabine will be 1 g/m^2 per day x 5 days and the second dose level will be 2 g/m^2 per day x 5 days. If the first dose level is not tolerated the study will stop since cytarabine 1 g/m^2 per day x 5 days is the lowest dose generally used in this setting. If the first dose level is tolerated but the second dose level exceeds the MTD, an intermediate dose level, 1.5 g/m^2 per day x 5 days will be evaluated.

In the Phase 1 portion, dose limiting toxicity (DLT) will be assessed for each subject up to the end of Cycle 1 of the sequential DACOGEN - cytarabine treatment. Subjects will be enrolled into Phase 1 using a "rolling 6" design[39] that determines the next subject's dose level of cytarabine based upon the number of subjects evaluable at the current dose level, how many subjects had DLTs, and how many subjects have safety data pending. There will be no intra-subject dose escalation. A minimum of 2 subjects and up to 6 subjects will be enrolled at each dose level. Each subject may receive 4 cycles of sequential treatment unless criteria for treatment discontinuation are reached sooner.

The Phase 2 portion of the study will be an extension of the Phase 1 portion and treat subjects with DACOGEN as a 1-hour IV infusion of 20 mg/m^2 once daily for 5 consecutive days on Days 1 to 5 followed by cytarabine at the MTD (determined in Phase 1) over a 4 hour IV infusion daily for 5 consecutive days (Day 8 to Day 12). Cycles are 28 days. Four cycles of sequential treatment are to be administered unless criteria for treatment discontinuation are reached sooner.

The Continuation Phase of the study will treat subjects with DACOGEN as a single agent; a 1-hour IV infusion of 20 mg/m^2 once daily on Days 1 to 5 of a 28-day cycle.

EFFICACY EVALUATIONS/ENDPOINTS

Efficacy evaluations will be performed on Day 28 of each cycle or within 8 days of the start of the next cycle. Response will be assessed using International Working Group (IWG) criteria[6]. The best response from up to 4 cycles of sequential treatment for each subject in the Phase 2 portion of the study will be used to determine the primary endpoint, response rate of CR + CRi. To be evaluable, subjects must complete at least 2 cycles of the sequential treatment and have at least 1 post-baseline disease assessment unless subjects discontinued treatment before Cycle 2 with disease progression or response (CR, CRi, or PR). Other efficacy endpoints include duration of response for subjects who achieve CR, CRi, overall response rate (CR + CRi + PR), OS, and EFS.

PHARMACOKINETIC EVALUATIONS

In Phase 1 and Phase 2, serial whole blood samples (0.5mL each) for PK will be obtained on Day 5 of Cycle 1 for determination of decitabine plasma concentrations. Cytarabine PK parameters will not be assessed. In subjects whose course of routine treatment includes sampling of CSF, a portion of that sample may be assessed for decitabine drug levels.

BIOMARKER EVALUATIONS

Biomarker evaluations will include DNA methylation analyses, DNA mutational analyses, gene expression, and micro RNA analyses.

SAFETY EVALUATIONS

The study will include the following evaluations of safety: adverse events (AEs), clinical laboratory tests (including hematology panel and serum chemistry panel), vital sign measurements (including temperature, heart rate, and blood pressure), physical examinations, and assessment of performance status.

In the Phase 1 portion of the study, the MTD for cytarabine is based on the number of subjects experiencing a dose limiting toxicity (DLT) by the end of Cycle 1. A non-hematological DLT is defined as: any Grade ≥3 toxicity that persists for >5 days or any Grade 2 toxicity that persists for >7 days and that is intolerable to the

subject. A hematological DLT is defined as Grade 4 neutropenia or thrombocytopenia due to a hypoplastic bone marrow at Day 42, in the absence of malignant infiltration. The nominal duration of each cycle will be 28 days. However, patients who have not experienced bone marrow recovery at Day 28 will be followed up to Day 42. Failure of marrow recovery (improvement to Grade 3) by Day 42 will be considered a DLT. The maximum duration of Cycle 1 will therefore be 42 days.

The decision to escalate or de-escalate cytarabine dose levels and the identification of the MTD will be the responsibility of a Study Evaluation Team (SET) that will convene periodically based on the number of evaluable patients and the occurrence of DLTs. The SET consists of the sponsor's statistician and clinician and other members as needed, eg, clinical pharmacologist, safety physician. The SET will also contain the lead investigator or designee from each country where the study is being conducted.

STATISTICAL METHODS

The safety population comprises subjects who signed the informed consent form (ICF) and received at least 1 dose of any study drug. The efficacy population is the subset of the safety population consisting of subjects who are evaluable for disease response. Subjects who withdraw prior to the completion of 2 cycles for reasons other than disease progression or response (CR, CRi, or partial response [PR]) and do not have at least 1 post-baseline disease assessment will be considered non-evaluable for response. Where appropriate, summaries (demographic, baseline characteristics, efficacy, and safety) will be presented for the Phase 1 part of the data, the Phase 2 part of the data, and data of the 2 phases combined.

The Phase 1 portion of the study will enroll up to 18 evaluable subjects (if the intermediate cytarabine dose is used), depending on when the MTD is determined. The Phase 2 portion of this study will include at least 15 evaluable subjects and is aimed to provide initial efficacy and additional safety data for the sequential administration of DACOGEN and cytarabine.

The primary efficacy endpoint is the response rate of CR + CRi for evaluable subjects from the Phase 2 part of the study. Statistical analyses include the percent of subjects who achieve a CR or CRi and the 95% confidence interval. The analyses are descriptive with the aim of assisting decision making for further clinical development of the sequential combination therapy. The best response observed at any time point during the 4 cycles of study treatment will be used. The response rate for subjects from the Phase 1 part of the study, and from Phase 1 and Phase 2 parts combined will also be summarized.

Duration of CR + CRi, overall response rate (CR + CRi + PR), event-free survival, and overall survival will be summarized. These summaries are also based on data of the Phase 2 part of the study. Where appropriate, these summaries will be performed on data from the Phase 1 part of the study and Phase 1 and Phase 2 parts combined.

TIME AND EVENTS SCHEDULE

Period	Screen	Sequential Treatment Cycles (up to 4)								DACOGEN only cycles, Continuation		
Day	Day -14 to 0	Day 1	Day 1-5	Day 5	Day 8	Day 8-12	Day 22	Day 28 or later but within 8 days of start of next cycle	End of Sequential Treatment Visit[b]	Q28 Days	End of Treatment Visit[c]	Follow-up[d]
Study Procedures												
Screening/Administrative												
Informed consent/assent[a]	X											
Inclusion/exclusion criteria	X											
Medical & treatment history and demographics[e]	X											
Pregnancy test	X											
Study Drug Administration												
Registration	X											
Dispense/administer study drug[f]			X			X				X		
Drug accountability			X			X				X		
Safety Assessments												
Physical examination and Performance Status[g,h]	X	X							X			
Safety assessment[i]			X			X	X		X	X	X	
Cardiac assessment[j]	X								X			
Efficacy Assessments												
Bone Marrow Aspirate[k]	X							X	X	X[l]		
Response assessment by IWG criteria[m]								X	X	X[l]		
Clinical Laboratory Assessments												
Hematology[n], including peripheral blast counts	X	X		X[o]	X		X[o]	X	X	X[p]	X	
Chemistry[q]	X	X							X		X	
Cytogenetics / molecular genetic characterization	X											
Pharmacokinetics												
Pharmacokinetics[o, r]				X								

Period	Screen	Sequential Treatment Cycles (up to 4)								DACOGEN only cycles, Continuation		
Day	Day -14 to 0	Day 1	Day 1-5	Day 5	Day 8	Day 8-12	Day 22	Day 28 or later but within 8 days of start of next cycle	End of Sequential Treatment Visit[b]	Q28 Days	End of Treatment Visit[c]	Follow-up[d]
Study Procedures												
Biomarkers:												
Whole Blood[s] – DNA methylation/ mutation	X				X			X				
Whole Blood[t] – Gene Expression, micro RNA Profiling	X				X			X				
Ongoing Subject Review												
Concomitant therapy	→	→	→	→	→	→	→	→	→	→	→	
Adverse events	→	→	→	→	→	→	→	→	→	→	→	

Footnotes:

a) By parent/legal guardian and/or subject as required by local regulation. Informed consent/assent needs to be in place prior to first study-specific screening assessment but is not considered as a screening assessment.

b) The End of Sequential Treatment Visit occurs at the end of the last sequential treatment cycle (or within 7 days thereafter).

c) The End of Treatment Visit occurs 30 +/- 5 days after last dose of DACOGEN plus cytarabine or single agent DACOGEN as part of this study whichever is later in both Phase 1 and 2.

d) Follow-up is to include recording of any late-occurring, potentially study drug-related adverse events, date(s) of any further treatment, drugs, and doses used and date of death, and should occur every 3 months for a maximum of 3 years after the last subject is enrolled or until 80% of patients are deceased, whichever occurs first. This is the assessment of long-term toxicity.

e) To include date of initial diagnosis, prior treatments, dates of prior treatments, response, and response duration

f) DACOGEN is administered on Days 1-5 at 20 mg/m^2 per day and cytarabine on Days 8-12 at the protocol defined dose.

g) Complete physical during screening (including vital signs ie, temperature, blood pressure, and pulse/heart rate) and at end of treatment. Limited examination focused on signs and symptoms at other times. Performance status (Karnofsky or Lansky) is evaluated prior to start of each cycle.

h) Height prior to Cycle 1 and weight prior to each cycle to determine body surface area

i) Safety assessment at each visit during treatment to include signs and symptoms of disease, adverse events, and any other changes in condition noted.

j) Fractional shortening ≥ lower limit of normal (29%) or LVEF (>58%) by echocardiogram (preferred). Results obtained more than 14 days prior to enrollment are acceptable provided no potentially cardiotoxic medications were administered between that evaluation and Cycle 1 Day 1.

k) Bone marrow aspirates will be performed at the end of Cycle 1 of sequential treatment (Day 28 or within 8 days of the start of the next cycle), the end of Cycle 2 if the subject did not achieve a CR at the end on Cycle 1, at the end of sequential treatment, or at any time disease progression is suspected. For Phase 1, bone marrow aspirates at end of Cycle 1 should be obtained no later than Day 42 in order to determine potential dose limiting toxicity. If available, a portion of the bone marrow aspirate collected at Screening and at end of the first Cycle will be used for DNA methylation/ mutation assessment, gene expression, and micro RNA analyses.

l) Results should be recorded if a bone marrow aspirate is obtained as part of standard clinical care.

m) Response assessment is performed at time at which bone marrow aspirate is obtained.
n) Hemoglobin, platelet count, white blood cell count, absolute neutrophil count (ANC), peripheral blast count
o) First cycle only
p) For the DACOGEN continuation period, hematology samples are obtained on Day 1 of each cycle prior to drug administration.
q) To include Na^+, K^+, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, serum uric acid
r) 0.5 mL whole blood to be obtained (blood should not be collected through the same line through which decitabine is infused, see Section 9.2.3) at; pre-infusion, 0.5 h during infusion, end of infusion, +5 min, +0.5h, +1h, and +2h after end infusion. Samples will be collected from Phase 1 and Phase 2 subjects. 0.5 ml of cerebrospinal fluid (CSF) will be collected for PK analysis when/if CSF is obtained as part of routine medical care except at screening.
s) Whole blood sample (2 mL) for DNA methylation pattern and DNA mutation determination at screening, prior to drug administration on Day, 8, and at the end of Cycle 1. This sample may also be used for gene expression and micro RNA analysis in the event only one biomarker blood sample can be drawn.
t) Whole blood (2.5 mL) for gene expression profiling and micro RNA analysis at screening, prior to drug administration on Day 8, and at the end of Cycle 1.

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration x time curve
BM	bone marrow
BMT	bone marrow transplant
BSA	body surface area
Cl	clearance
C_{max}	maximum plasma concentration
CNS	central nervous system
CNS3	central nervous system disease category 3
CRF	case report form (paper or electronic as appropriate for this study)
CR	complete Response
CRi	complete Response incomplete hematological recovery
CSF	cerebrospinal fluid
CTCAE	common terminology criteria for adverse events
DLT	dose-limiting toxicity
eCRF	electronic case report form
eDC	electronic data capture
EU	European Union
EC	ethics committee
EFS	event-free survival
FAB	French-American-British
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	informed consent/assent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IVRS	interactive voice response system
IWG	International Working Group
IWRS	interactive web response system
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LV	left ventricular
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	overall survival
PB	peripheral blood
PD	pharmacodynamic
PIP	Pediatric Investigational Plan
PK	pharmacokinetic
PQC	Product Quality Complaint
PR	partial response
SD	stable disease
SET	Study Evaluation Team
SmPC	summary of product characteristics
t_{max}	time of maximum plasma concentration
UNL	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

DACOGEN®, the formulated product of the active agent decitabine (5-aza-2'-deoxycytidine), was developed in the 1960's as a cytotoxic analog of 2'-deoxycitidine. DACOGEN has been shown to be a DNA hypomethylating agent at doses currently used in the clinic.[2,21,32] DACOGEN is approved in the US and over 35 countries for the treatment of patients with myelodysplastic syndrome (MDS) and in the EU and 4 other countries (at the time of writing this protocol) for the treatment of patients aged 65 years and above with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organization (WHO) classification, who are not candidates for standard induction chemotherapy. More information regarding the basis of approval for the treatment of older adults with AML please refer to the Investigator's Brochure.[11]

This protocol incorporates recommendations from the Pediatric Development Committee of the European Medicines Agency from an established Pediatric Investigational Plan (PIP) initially approved on 7 April 2010 and most recently modified on 28 March 2012. As part of the PIP, an initial Phase 1-2 study investigates the pharmacokinetics (PK), safety, and efficacy of a sequential administration of DACOGEN and cytarabine. If this combination is found to be safe and effective, a randomized, comparative, cooperative group Phase 3 study will be designed. This protocol defines the initial Phase 1-2 study.

For the most comprehensive nonclinical and clinical information regarding DACOGEN, refer to the latest version of the IB for DACOGEN.[11]

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

1.1.1. Childhood Acute Myeloid Leukemia

Approximately 20% of childhood leukemias are of myeloid origin and represent a spectrum of hematopoietic malignancies.[40] The majority of myeloid leukemias are acute and the remainder includes chronic and/or subacute myeloproliferative disorders such as chronic myelogenous leukemia (CML) and juvenile myelomonocytic leukemia (JMML), as well as myelodysplastic syndromes.

Acute myeloid leukemia (AML) is defined as a clonal disorder caused by malignant transformation of a bone marrow-derived, self-renewing myeloid stem cell or progenitor, which demonstrates a decreased rate of self-destruction as well as aberrant differentiation. These events lead to increased accumulation of these malignant myeloid cells in the bone marrow and other organs. To be called acute myeloid leukemia, the bone marrow usually must include greater than 20% leukemic blasts.[6,45]

AML in children is comparatively rare with an estimated incidence of between five and seven cases per million people per year, with a peak incidence occurring at approximately 2 years of age. Incidence reaches a low point at an age of approximately 9 years, then increases to nine cases per million during adolescence and remains relatively stable until age 55 years.[7,18,49] The development of AML is associated with a variety of predisposition syndromes that result from chromosomal imbalances or instabilities, defects in DNA repair,

altered cytokine receptor or signal transduction pathway activation, as well as altered protein synthesis.[28,50]

There is a high concordance rate of AML in identical twins, which is believed to be in large part a result of shared circulation and the inability of one twin to reject leukemic cells from the other twin during fetal development.[19] There is an estimated twofold to fourfold risk of fraternal twins both developing leukemia up to about age 6 years, after which the risk is not significantly greater than that of the general population.[17,25]

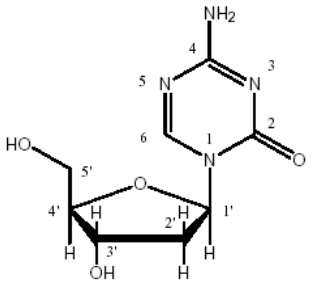
For AML, the 5-year survival rate for children younger than 15 years increased from less than 20% during the period from 1975 to 1978 to 58% during the period from 1999 to 2002. For older adolescents (age 15-19 years), outcome was similar to that of younger children from 1975 to 1978 but has remained lower at 35% to 40% since the late 1980s.[41] There remains a significant proportion of patients who relapse early or fail to respond to initial treatment and require reinduction therapy with the ultimate aim of achieving a complete response that would enable stem cell transplantation to occur. The prognosis for a child with recurrent or progressive AML is generally poor. Approximately 50% to 60% of relapses occur within the first year following diagnosis, with most relapses occurring by 4 years from diagnosis. The vast majority of relapses occur in the bone marrow, with central nervous system (CNS) relapse being very uncommon.[47] The length of the first remission is an important predictor of the potential to attain a subsequent remission. Children with a first remission of less than 1 year have substantially lower rates of second remission compared to children whose first remission is greater than 1 year (approximately 50%–60% versus 70%–90%, respectively). Survival for children with shorter duration of first remission is also substantially lower (approximately 10%) compared to children for whom first remission exceeds 1 year (approximately 40%).[43,46,48]

Current treatment options for relapsed or refractory AML are limited, a number of agents are used as reinduction therapy an attempt to induce second remission and facilitate allogeneic stem cell transplant and include cytarabine, fludarabine and anthracycline based approaches. Guidelines suggest that often the preferred option is to enter patients into clinical studies. The use of some form of intrathecal chemotherapy as CNS-directed treatment is considered a standard part of the treatment for AML, irrespective of CNS involvement.

1.1.2. Rationale for DACOGEN Treatment of Patients with AML

Decitabine, the active substance in the formulated product DACOGEN, is a 2'-deoxycytidine nucleoside analog in which the #5 carbon of the nucleoside base has been modified to nitrogen. The generic name is decitabine or 5-aza-2'-deoxycytidine. The trade name is DACOGEN for Injection. The chemical structure is shown in Figure 1.

Figure 1: Chemical Structure of Decitabine



The mechanism of action of decitabine is hypomethylation of DNA by irreversible inhibition of DNA methyltransferases. This inhibition leads to lower levels of methylated cytosine residues, a normally occurring epigenetic modification that transcriptionally silences gene expression. Treatment with decitabine leads to the re-expression of tumor suppressor gene products leading to cell differentiation, apoptosis, and senescence. Further details regarding the mechanism of action are provided in the IB.[11]

1.1.3. Nonclinical Studies Relevant to This Protocol

1.1.3.1. Preclinical Studies of Pediatric AML Explants

Studies have been conducted to characterize the effects of decitabine on the growth and cellular physiology of primary cultures of pediatric AML cell samples both in in vitro systems and in xenograft in vivo models. These studies examined decitabine alone and in combination with a standard chemotherapy agent for AML, cytarabine. Additionally, these cellular systems were used to measure pharmacodynamic effects (DNA hypomethylation) and investigate potential biomarkers for decitabine activity.

Decitabine alone and combinations of decitabine plus cytarabine produced antiproliferative effects in primary cultures of pediatric AML cells. Generally, the potency of cytarabine was greater than the potency of decitabine. Concurrent administration of decitabine and cytarabine did not appear to alter the antiproliferative potency of cytarabine, suggesting the 2 compounds, both cytosine analogs and utilizing similar activation pathways, do not interact. Although the cell cycle effects were somewhat variable across the individual primary pediatric AML cell cultures, the most consistent finding was an increase in apoptosis produced by combinations of decitabine and cytarabine as determined by flow cytometry analysis.[29]

In assessments of DNA methylation, a maximal inhibition of DNA methylation was observed at a concentration of 50 nM decitabine after 5 days of treatment. Gene expression profiling was examined in 5 patient samples. Each decitabine-treated sample (50 nM for 4 days) was compared to the corresponding PBS vehicle treated control. The only gene expression change exhibiting concordant changes in expression was BCL-2, which demonstrated increased expression post-treatment. The relevancy of this observation is unclear because the observation could reflect a selection of clones with higher levels of the anti-apoptotic protein BCL-2 that were resistant to the apoptotic effects of decitabine in vitro. Other changes in gene expression were variable across the 5 patient cell samples.[29]

Three pediatric AML samples that were evaluated in vitro could be propagated in immunocompromised mice allowing for the in vivo study of therapeutic agents. Decitabine and cytarabine were evaluated as a daily intraperitoneal administration for 5 days as single agents, simultaneous administration, or sequential administration. Single agent decitabine and cytarabine reduced tumor burden; simultaneous treatment with decitabine plus cytarabine had a greater anti-leukemic effect but was associated with increased host toxicity. Sequential treatment with decitabine and cytarabine showed increased effectiveness compared to single agent administration however, without increased toxicity. There was no obvious advantage of the sequence of administration of the agents (decitabine followed by cytarabine versus cytarabine followed by decitabine). These results provide nonclinical evidence favoring sequential administration of decitabine and cytarabine over simultaneous administration. Gene expression profiling was explored in the xenograft tumor samples to identify potential markers of treatment response but no clear biomarker for response was identified.[30]

1.1.3.2. Sensitivity and Resistance of Combinations of Decitabine and Cytarabine

These experiments focused on determining whether combinations of decitabine and cytarabine led to reduced levels of decitabine triphosphate (the active decitabine moiety that is incorporated into DNA) and reduced antiproliferative effects of either agent based upon the shared intracellular pathways for metabolic activation and incorporation into DNA. HL-60 human promyelocytic leukemia cells were selected for study based on pilot studies pertaining to the detection of decitabine triphosphate. Concurrent administration of cytarabine (IC_{50} concentration, 52nM) with decitabine did not affect intracellular decitabine triphosphate levels. Pretreatment with cytarabine for 72 hours prior to incubation with decitabine did not decrease decitabine triphosphate levels. A trend towards increased decitabine triphosphate was observed.[3] Additionally, pretreatment with cytarabine for 72 hours prior to decitabine led to a moderate decrease in global methylation.[13]

Cell growth studies revealed that concomitant treatment with cytarabine and decitabine did not alter the relative antiproliferative potency (IC_{50}) of either compound. Pretreatment with cytarabine for 72 hours prior to decitabine treatment did not alter the relative potency of decitabine. Pretreatment with decitabine for 72 hours prior to treatment with cytarabine produced an antiproliferative effect that carried over to the cytarabine incubation despite a 72 hour washout period. However, a concentration-related inhibition of cell proliferation was still observed with the addition of cytarabine and the relative potency did not appear to be altered.[14]

In conclusion, studies in the HL-60 promyelocytic leukemia cell line indicated that pretreatment with decitabine or cytarabine did not reduce the effectiveness of subsequent treatment of HL-60 cells with the agents under study.

1.1.3.3. Rat Juvenile Toxicology

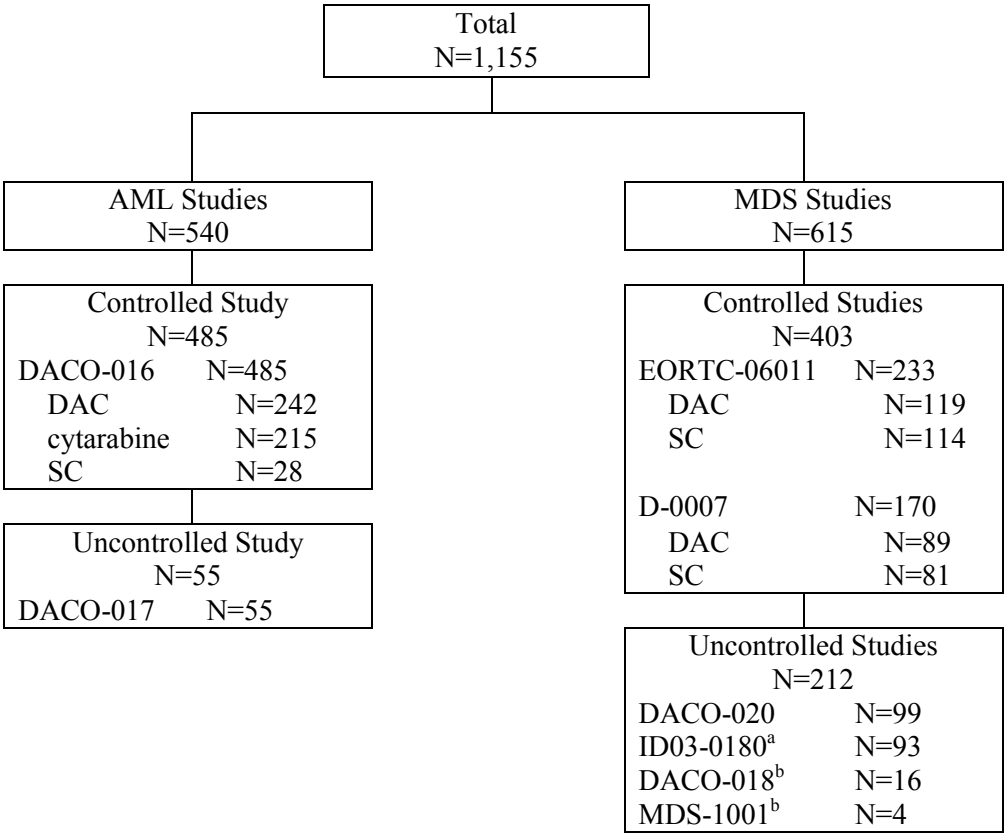
In the neonatal/juvenile rat, subcutaneous/IV (bolus) dosing of decitabine starting on Day 7 or 11 of age and lasting until Day 35 of age,[12] resulted in dose related inhibition of blood cell formation in the bone marrow and histopathological changes in the lymphoid tissue and bone marrow. At the end of the recovery period until at least Day 70 of age, minimal focal/multifocal seminiferous tubular atrophy/degeneration was recorded in the testes in the

highest dose group (subcutaneous/IV: 5.4/1.8 mg/m^2 per day [0.9/0.3 mg/kg per day]). Growth and the age of attainment of sexual maturity were also affected. The highest dose tested was the no observed effect level (NOEL) for survival, neurobehavioral development, and reproductive capacity.

1.1.4. Clinical Studies

The development program for DACOGEN focused on the treatment of older patients with MDS and AML as well-characterized patient populations with a high unmet medical need. Figure 2 illustrates the studies and corresponding number of subjects evaluated in Company studies. In total, 1,155 subjects were entered in the clinical studies (2 studies in AML and 4 studies in the closely-related condition, higher-risk MDS). Efficacy of DACOGEN in AML is evaluated in the Phase 3 study DACO-016 and the Phase 2 study DACO-017. Patients who had received prior therapy for AML as well as patients with favorable cytogenetics or acute promyelocytic leukemia were excluded from these studies. Baseline parameters of demographics and subject and disease characteristics were very similar between the 2 studies with the exception of age. Study DACO-016 enrolled subjects 65 years of age or older, whereas Study DACO-017 enrolled subjects 60 years of age or older.

Figure 2: Number of Subjects Participating in DACOGEN Clinical Studies



AML=acute myeloid leukemia; DAC=DACOGEN; MDS=myelodysplastic syndromes; SC=supportive care.

[a] ID03-0180 includes only those subjects who were treated with DACOGEN 20 mg/m^2 IV daily for 5 consecutive days every 4 weeks.

[b] DACO-018 and MDS-1001 studies were used for pharmacokinetic determinations only.

The AML studies demonstrated clinical improvements for older subjects treated with DACOGEN through an increased response rate, prolonged PFS and EFS, and a survival improvement over standards of care while maintaining a well-defined safety profile characterized predominantly by myelosuppression or consequences of myelosuppression that can be managed with routine supportive care.

1.1.4.1. Human Pharmacokinetic Studies

The population PK parameters of decitabine in adults were pooled from 3 clinical studies (DACO-017 [n=11], DACO-020 [n=11] and DACO- 016 [n=23]) utilizing the 5-Day regimen (20 mg/m^2 IV infusion for 1-hour x 5 days every 4 weeks) and 1 study, DACO-018 (n=12), utilizing the 3-Day regimen (15 mg/m^2 IV infusion over 3-hours every 8 hours x 3 days every 6 weeks) in MDS or AML patients. For the 5-Day regimen, decitabine PK was evaluated on the fifth day of the first treatment cycle. Total dose per cycle was 100 mg/m^2. For the 3-Day regimen, decitabine PK was evaluated after the first dose of each dosing day of the first treatment cycle. Total dose per cycle was 135 mg/m^2.

Distribution

The PK of decitabine following intravenous administration as a 1-hour (5-Day regimen) or 3-hour (3-Day regimen) infusion was described by a linear two-compartment model, characterized by rapid elimination of the drug from the central compartment and by relatively slow distribution from the peripheral compartment. For a typical patient (weight 70 kg/body surface area 1.73 m^2) the decitabine PK parameters are listed in Table 1 below.

Table 1: Summary of Population PK Analysis for a Typical Patient (5-Day and 3-Day Regimen)

	5-Day Regimen		3-Day Regimen	
Parameter	Predicted Value	95% CI	Predicted Value	95% CI
C_{max} (ng/mL)	107	88.5 – 129	42.3	35.2 – 50.6
AUC_{cum} (ng·h/mL)	580	480 – 695	1161	972 – 1390
$t_{1/2}$ (min)	68.2	54.2 – 79.6	67.5	53.6 – 78.8
Vd_{ss} (L)	116	84.1 – 153	49.6	34.9 – 65.5
CL (L/h)	298	249 – 359	201	168 – 241

AUC=area under the plasma concentration-time curve; CL=total body clearance; C_{max}=maximum observed concentration; $t_{1/2}$=terminal elimination half-life; Vd_{ss}=mean volume of distribution at steady state
Source: Population PK Report[34]

Decitabine exhibits linear PK and following intravenous infusion, steady-state concentrations are reached within 0.5 hour. Based on model simulation, PK parameters were independent of time (ie, did not change from cycle to cycle) and no accumulation was observed with this dosing regimen. Plasma protein binding of decitabine is negligible (<1%). Decitabine mean volume of distribution at steady state (Vdss) in cancer patients is large indicating distribution of the drug into peripheral tissues. There was no evidence of dependencies on age, creatinine clearance, total bilirubin, or disease.

Metabolism

Intracellularly, decitabine is activated through sequential phosphorylation via phosphokinase activities to the corresponding triphosphate, which is then incorporated into DNA by the DNA polymerase. Based on in vitro metabolism data and human mass balance study results, the cytochrome P450 system is not involved in the metabolism of decitabine. The primary

route of metabolism is likely through deamination by cytidine deaminase in the liver, kidney, intestinal epithelium, and blood. Results from the human mass balance study showed that unchanged decitabine in plasma accounted for approximately 2.4% of total radioactivity in plasma. The major circulating metabolites are not believed to be pharmacologically active. The presence of these metabolites in urine together with the high total body clearance and low urinary excretion of unchanged drug in the urine (~4% of the dose) indicate that decitabine is appreciably metabolized in vivo. In addition, in vitro data show that decitabine is a poor P-gp substrate.

Elimination

Mean plasma clearance following intravenous administration in cancer subjects was >200 L/h with moderate inter-subject variability (Coefficient of Variation [CV] is approximately 50%). Excretion of unchanged drug appears to play only a minor role in the elimination of decitabine. Results from a mass balance study with radioactive ^{14}C-decitabine in cancer patients showed that 90% of the administered dose of decitabine (4% unchanged drug) is excreted in the urine.

Pediatric Data

Preliminary data from 10 subjects of a Phase 1-2 study in pediatric patients with AML ages 2 to 16 years old indicated that decitabine PK parameters were consistent with known adult PK profiles.[15]

1.1.4.2. Efficacy/Safety Studies

1.1.4.2.1. Efficacy of DACOGEN in Adult Subjects with Acute Myeloid Leukemia

Study DACO-016 (CSR ref) was the largest randomized, active controlled, Phase 3 study in older (≥65 years) patients with AML conducted to date with 485 subjects enrolled. The main objective was to compare DACOGEN, administered at a dose of 20 mg/m^2 once daily for 5 consecutive days every 4 weeks (5-Day regimen), with Treatment Choice (TC) consisting of the subject's choice (with physician's advice) of the current standard care options of low-dose cytarabine (20 mg/m^2 once daily for 10 consecutive days every 4 weeks) or supportive care.

The primary analysis showed a clinically meaningful trend for improved OS for subjects treated with DACOGEN although it did not reach statistical significance. Subsequent analysis of survival data with one year of additional data showed a stronger treatment effect for DACOGEN. The median overall survival (OS) remained 5.0 months in the TC arm and 7.7 months in the DACOGEN arm with an improved hazard ratio of 0.82 (95% CI: 0.68, 0.99), and nominal p=0.0373. Results for other endpoints showed significant improvements for DACOGEN-treated subjects in response rates, PFS and EFS. These results were consistent with those obtained in the Phase2 study, DACO-017. Further details are provided in the IB.[11]

1.1.4.2.2. Safety of DACOGEN in Adult Subjects with Acute Myeloid Leukemia

DACOGEN safety was evaluated using integrated datasets from the AML studies DACO-016 and DACO-017, 3-Day DACOGEN dosing in MDS studies D-0007 and EORTC-06011, and 5-Day dosing in MDS studies ID03-0180 and DACO-020 (See Figure 2). A total of 697 subjects treated with DACOGEN were evaluated for safety in clinical studies. The median duration of treatment with DACOGEN in subjects with AML was almost twice as long (4.14 months) compared with cytarabine treatment (2.35 months). Longer treatment duration for DACOGEN-treated subjects was a reflection of treatment benefit and tolerability.

The most frequently reported adverse events (AEs) in subjects treated with DACOGEN were myelosuppression (neutropenia, thrombocytopenia, and anemia) and consequences of myelosuppression (infections, bleeding events, and fatigue) which were reported at a higher (up to 15%) frequency compared with cytarabine treatment in subjects with AML (Table 2).

Table 2: Most Frequently Reported Adverse Events in the Integrated AML Studies DACO-016 and DACO-017

Preferred Term	Supportive Care	Cytarabine	DACOGEN
Pyrexia	21%	39%	48%
Thrombocytopenia	14%	40%	41%
Anaemia	14%	34%	38%
Nausea	17%	31%	33%
Febrile neutropenia	0%	26%	34%
Diarrhoea	17%	24%	31%
Neutropenia	3%	23%	32%

Note: Percentages were calculated with the number of subjects in each group as the denominator.
Note: Incidence was based on the number of subjects experiencing at least 1 adverse event, not the number of events.
Source: Summary of Clinical safety\Table18

The longer treatment duration led to a longer reporting period for adverse events for DACOGEN-treated subjects compared to cytarabine-treated subjects, and this should be considered in safety comparisons between these groups. In the supportive MDS studies, the median treatment duration was 7.34 months for the 5-Day studies and 5.65 months for the 3-Day studies. In all the DACOGEN treatment groups there were similar median dose intensities: in AML studies, 23.7 mg/m^2 per week, in MDS 5-Day studies, 21.2 mg/m^2 per week, and in MDS 3-Day studies, 21.1 mg/m^2 per week.

No new safety signals were identified in the AML studies compared with previous experience with DACOGEN in patients with MDS either in clinical studies or postmarketing experience. Further details of the safety of DACOGEN are provided in the IB.[11]

1.2. Combination Therapy

Cytarabine

Study DACOGENAML2004 investigates the sequential administration of DACOGEN treatment followed by cytarabine. Cytarabine is indicated as an induction chemotherapy regimen for patients with AML and several other leukemias and lymphomas as a single agent or in combination with other antineoplastic agents. Cytarabine is a potent bone marrow suppressing agent resulting in hematological toxicities of cytopenias and anemia. Other

toxicities include gastrointestinal effects (nausea, vomiting, diarrhea, and anorexia), fever, alopecia, and neurotoxicity. For further information regarding cytarabine refer to the Summary of Product Characteristics (SmPC; http://www.medicines.org.uk/EMC), or the SmPC for cytarabine applicable to the local country.

Cytarabine is one of the most common agents used to treat AML and other hematological malignancies. Combinations of cytarabine are often used with other chemotherapeutic agents such as anthracyclines and results in response rates in the pediatric AML population of between 17% and 69%.[16,24] Treatment of patients with AML after first or later relapse is confounded by the accumulating toxicity of certain chemotherapeutic agents such as the anthracyclines. Other combination therapies are needed to address this unmet need. The preclinical experiments described in Section 1.1.1 suggest that the sequential administration of DACOGEN and cytarabine may provide antileukemic activity in pediatric patients, hence cytarabine was chosen as the agent to be combined with DACOGEN for this study.

1.3. Overall Rationale for the Study

A significant proportion of pediatric AML patients relapses early or fails to respond to initial treatment. They require reinduction therapy with the ultimate aim of achieving a CR that would enable stem cell transplantation. The prognosis for a child with recurrent or progressive AML is generally poor. Approximately 50% to 60% of relapses occur within the first year following diagnosis, with most relapses occurring by 4 years from diagnosis.[47]

Clinical and preclinical data suggest that sequential dosing of DACOGEN and cytarabine might be more effective than either agent used alone in refractory/relapsed pediatric AML. Preclinical data using human pediatric primary xenografts suggest the sequence of DACOGEN followed by cytarabine would be effective in patients with relapsed or refractory disease.[30] Additionally, a Phase 1 study of epigenetic priming prior to treatment with standard "7 + 3" induction therapy showed that 20 mg/m^2 of DACOGEN could safely be given for 5 days prior to cytarabine (100 mg/^{2} per day x 7 days) and daunorubicin (60 mg/m^2 per day x 2 days).[35]

Despite commonality between the diagnosis and treatment of AML for children and adults there are significant differences between the diagnosis and treatment of children and adults. One of the principle challenges in investigating new approaches to treating pediatric patients is that they represent a very broad spectrum, from infants through to near adults. While in principle the treatment of younger children for example is no different to that of older individuals, the immaturity of organs in infants for example can confer a certain susceptibility to toxicity due to the differing pharmacokinetic and pharmacodynamic properties of certain drugs. In the case of cytarabine there is evidence to suggest that children younger than 2 years old may exhibit reduced cytarabine clearance.[31]

The rational for this study is to examine the safety and efficacy of DACOGEN in sequential administration with cytarabine, which is the backbone of current standard combination treatments for relapsed/refractory pediatric AML. It is therefore necessary to first identify the dose of cytarabine that can be safely administered following DACOGEN treatment.

If the sequential combination can be safely administered with a clinically interesting level of activity, this would provide the basis for further evaluation in this indication.

2. OBJECTIVES AND HYPOTHESES

2.1. Objectives

Primary Objectives

The primary objectives of the Phase 1 portion of Study DACOGENAML2004 are:

- to determine the maximum tolerable dose (MTD) of cytarabine (up to 2 g/m^2 per day x 5) that can be administered on Days 8-12 following treatment with DACOGEN 20 mg/m^2 per day on Days 1-5 of a 28-day cycle.
- to determine PK parameters including maximum plasma concentration (C_{max}), Area under the concentration x time curve (AUC), time to maximum plasma concentration (t_{max}), and clearance (Cl) of decitabine on Day 5 of Cycle 1.

The primary objective of the Phase 2 portion of Study DACOGENAML2004 is to determine the response rate (CR + CRi) in children with relapsed or refractory AML when treated with DACOGEN 20 mg/m^2 per day on Days 1-5 followed by cytarabine at the determined MTD on Days 8-12 for up to 4 cycles of treatment.

Secondary Objectives

The secondary objectives are to evaluate the safety profile of DACOGEN 20 mg/m^2 per day administered on Days 1 to 5 followed by cytarabine on Days 8 to 12 for up to 4 cycles of therapy and to describe the duration of CR + CRi and evaluate the overall response (CR + CRi + PR) to treatment

Other objectives are to determine event-free survival (EFS) and overall survival (OS) for subjects treated with the sequential administration of DACOGEN and cytarabine, to explore the pharmacodynamic effects of DACOGEN with respect to DNA hypomethylation status and gene expression, and to explore predictive biomarkers for response to DACOGEN and cytarabine sequential treatment. The plasma PK profile of decitabine is a secondary endpoint in the Phase 2 portion of the study and levels of decitabine in the cerebrospinal fluid (CSF) will be evaluated if samples are collected as part of other required medical care.

2.2. Hypotheses

The hypothesis to be tested in the Phase 1 portion of this study is that DACOGEN administered at 20 mg/m^2 per day for 5 consecutive days followed by at least 1 g/m^2 per day (but not more than 2 g/m^2 per day) of cytarabine on Days 8 to 12 can safely be given to children with relapsed or refractory AML.

The Phase 2 portion of the study is based on the hypothesis that the sequential administration of DACOGEN and cytarabine induces responses in pediatric patients with relapsed/refractory AML. It does not have formal hypothesis testing but is aimed to obtain initial efficacy and additional safety data of the sequential administration of DACOGEN and cytarabine.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is an open-label, multicenter Phase 1-2 study to evaluate safety, PK, and clinical activity of DACOGEN in sequential administration with cytarabine in children ages 1 month to less than 18 years with relapsed or refractory AML. The study will determine the MTD of cytarabine that can be given on Days 8 to 12 following DACOGEN 20 mg/m^2 per day on Days 1 to 5 (Phase 1) and the response rate to this combination (Phase 2). Pharmacokinetic sampling will occur, at predetermined timepoints on Day 5 of Cycle 1 in the Phase 1 and the Phase 2 portion of the study.

3.1.1. Phase 1 Portion of DACOGENAML2004

For the Phase 1 portion of the study, a "rolling 6" design[39] is used. The total number of participants is dependent upon the number of cytarabine dose levels tested; the maximum number of which is 3 dose levels (1 g/m^2, 2 g/m^2, and 1.5 g/m^2) with a maximum of 18 evaluable subjects.

The MTD for cytarabine is based on the number of subjects experiencing a DLT by the end of Cycle 1. A non-hematological DLT is defined as: any Grade ≥3 toxicity that persists for >5 days or any Grade 2 toxicity that persists for >7 days and that is intolerable to the subject. A hematological DLT is defined as Grade 4 neutropenia or thrombocytopenia due to a hypoplastic bone marrow at Day 42, in the absence of malignant infiltration. The nominal duration of each cycle will be 28 days. However, patients who have not experienced bone marrow recovery at Day 28 will be followed up to Day 42. Failure of marrow recovery (improvement to Grade 3) by Day 42 will be considered a DLT. The maximum duration of Cycle 1 will therefore be 42 days.

The decision to dose escalate from the starting dose of 1 g/m^2 will be based on the number of subjects evaluable and the number pending evaluation during the first cycle. No dose escalation will occur unless a minimum of 3 subjects are fully evaluable with no dose limiting toxicity. If any additional subjects have been treated at that dose level, they must become evaluable before the dose can be escalated. The only exception is the setting in which 5 patients are evaluable, no DLT has been observed and data for one subject is incomplete making it impossible for the MTD to be exceeded. Further details of the "rolling-6" design and the determination of the MTD are provided in Section 6.3.

The decision to escalate or de-escalate dose levels and the identification of the MTD will be the responsibility of a Study Evaluation Team (SET) that will convene periodically based on the number of evaluable patients and the occurrence of dose limiting toxicities. The SET consists of the sponsor's statistician and clinician and other members as needed, eg, clinical pharmacologist, safety physician. The SET will also include the lead investigator or designee from each country where the study is being conducted. Further description of the SET and their responsibilities is provided in Section 11.9.

Subjects receiving any dose level of cytarabine in the Phase 1 portion of the study may receive 4 cycles of study treatment unless the subject meets criteria for treatment discontinuation (Section 10.2). In adults with AML, the best response was observed after a median of 4 cycles of single-agent DACOGEN. Once the MTD of cytarabine is determined,

subjects treated at doses other than the MTD for less than 4 cycles can elect to proceed with remaining cycles at the MTD. The Phase 1 portion of the study will end when the MTD of cytarabine (no more than 2 g/m^2 per day x 5 days) administered on Days 8-12 in sequential administration with DACOGEN (20 mg/m^2 on Days 1-5) has been determined and all subjects have been treated for up to 4 cycles. Subjects who completed up to 4 cycles of the sequential treatment can elect to receive single-agent DACOGEN in the Continuation Phase of the study, if in the treating physician's opinion it would be beneficial. In order to use subject data efficiently and reduce the number of subjects in the study, data from the 6 (or fewer) subjects who are treated at the MTD level in the Phase 1 portion may be included in the Phase 2 portion of the study.

3.1.2. Phase 2 Portion of DACOGENAML2004

The Phase 2 portion of the study will be an open-label, single arm study of the sequential administration of DACOGEN and cytarabine in at least 15 evaluable children with relapsed or refractory AML. Subjects who received the MTD of cytarabine for up to 4 cycles in the Phase 1 portion of the study and are evaluable will be included in the evaluation of the Phase 2 portion of the study. Subjects may elect to receive single-agent DACOGEN in the continuation portion of the study if, in the opinion of the treating physician, the subject would benefit.

The Phase 2 portion will utilize DACOGEN 20 mg/m^2 IV infusion over 1 hour on Days 1 to 5 and the dose of cytarabine determined in Phase 1 on Days 8-12. This regimen should be repeated for 4 cycles of treatment unless criteria for treatment discontinuation are reached.

There will be no independent data monitoring committee.

The primary efficacy endpoint will be the response rate, ie, CR + CRi (complete remission with incomplete blood cell count recovery) based on the evaluation up to the end of Cycle 4. Assessment of clinical response and disease progression will be conducted in accordance with the IWG response criteria.[6] Bone marrow aspirates will be performed at the end of Cycle 1 of sequential treatment (Day 28 or within 8 days of the start of the next cycle), the end of Cycle 2 if the subject did not achieve a CR at the end on Cycle 1, at the end of sequential treatment, or at any time disease progression is suspected. Safety assessments will include adverse event monitoring, physical examinations, clinical laboratory parameter (hematology and chemistry) monitoring, and assessment of performance status, as described in the Time and Events schedule.

The clinical cut off for the primary endpoint will occur 30 days after the last subject has completed sequential treatment.

Blood samples will be drawn for the assessment of pharmacokinetic parameters. Blood samples will also be collected for biomarker analyses to explore pharmacodynamics effects of DACOGEN as well as potential predictive markers for response to DACOGEN + Cytarabine treatment. Biomarkers planned to be analyzed include DNA methylation, gene expression changes, gene methylation profiling, gene mutation profiling, and micro RNA profiling. Blast counts and other hematological parameters will be monitored by local laboratories. All study evaluations will be conducted according to the Time and Events Schedule.

3.1.3. Continuation Phase of Study DACOGENAML2004

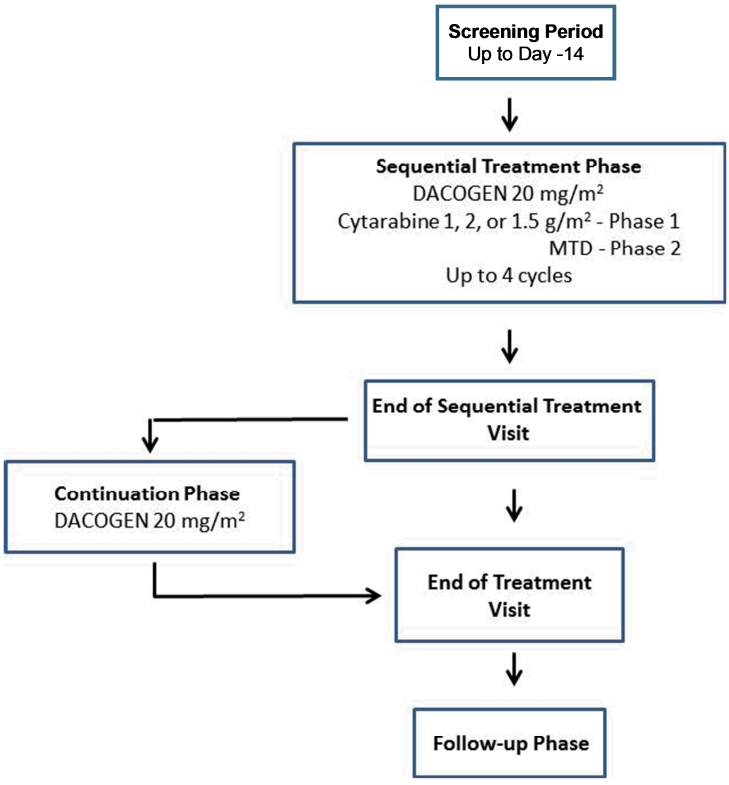
After completing 4 cycles of sequential DACOGEN - cytarabine treatment in either Phase 1 or Phase 2 of this study, subjects who, in the opinion of the treating physician, may benefit, can receive single agent DACOGEN at 20 mg/m^2 IV infusion over 1 hour on Days 1-5 every 28 days in the study Continuation Phase for as long as such treatment is considered beneficial. Additionally, subjects who discontinue DACOGEN - cytarabine sequential treatment may enter the Continuation Phase if, in the opinion of the treating physician, the subject would benefit. Subjects who start single agent DACOGEN will be followed for safety and efficacy until the treatment ends. Bone marrow aspirates will be performed only as clinically indicated and response assessments documented. The End of Treatment Visit should occur 30 days after the last dose of single agent DACOGEN after which the subjects will enter the Follow-up Phase of the study. In the event subjects continue to derive benefit at study end, DACOGEN will continue to be supplied by the Company.

3.1.4. Follow-Up Phase of Study DACOGENAML2004

Subjects who discontinue study treatment in the Phase 1, Phase 2, or Continuation Phase of the study will enter the Follow-up Phase. Follow-up assessments will occur every 3 months for long term safety, subsequent therapies, and survival until the end of study. The end of study is defined as 3 years after the last subject is enrolled or when 80% of the patients are deceased, whichever comes first.

A diagram of subject experience in this study is provided in Figure 3.

Figure 3: Schematic Overview of the Study



3.2. Study Design Rationale

Rationale for Sequential Therapy

The addition of a new agent to available regimens can mediate their clinical benefit on the premise that the combined agents have non-overlapping and synergistic mechanisms of action.

Cytarabine is a core component of initial and later therapy for patients with AML regardless of patient age. AML treatment guidelines indicate that therapy should combine an anthracycline with standard-dose cytarabine with or without other agents, high-dose cytarabine alone or combined with an anthracycline, asparaginase or etoposide or using the purine analogues, fludarabine or 2 chloro-deoxyadenosine combined with high-dose cytarabine, with or without an anthracycline and/or granulocyte-colony stimulating factor.[46]

The recent demonstration of a role for low dose DACOGEN for the treatment of older patients with AML creates the opportunity to explore the potential benefit of DACOGEN in younger age groups.[22] Limited data available from small clinical trials suggest that DACOGEN is active in pediatric patients with AML:

- Preliminary single agent Phase 2 data in very high risk relapsed pediatric AML patients showed that DACOGEN administered as a 20 mg/m^2 IV infusion on Days 1-10 (Q 28 days) produced antileukemic effects. Of 8 subjects treated (ages 2-26, median age 4 years) with DACOGEN, 3 subjects had a CR, complete remission with incomplete platelet recovery (CRp) or CRi, 3 subjects had a PR, 1 had stable disease and 1 had progressive disease. Median time to best response was 2.5 cycles and the drug was well tolerated with neutropenia as the most common toxicity with 2 serious infections in 24 cycles.[33]
- A Children's Oncology Group (COG) study enrolled 2 patients with relapsed or refractory AML (N=2) and acute lymphocytic leukemia (ALL; N=8) between 2002 and 2005. The starting dose of DACOGEN was 10 mg/m^2 daily on Days 1-5 and 8-12 of a 28-day cycle. The study was closed early due to poor accrual and lack of effect. (personal communication, Norman Lucayo, Stanford University, Stanford, CA, USA)
- In an ongoing randomized pediatric study in the US and Australia the first line treatment of children with daunorubicin, cytarabine, and etoposide either is or is not preceded with a 5 day priming period with DACOGEN. Efficacy (CR + CRi) is measured 3 weeks post induction therapy. Initial data from 24 subjects indicates similar CR + CRi rate in both arms, but longer time to platelet recovery for subjects with DACOGEN priming. Preliminary PK data are available for 21 subjects.[15]

Clinical and preclinical data suggest that sequential dosing of DACOGEN and cytarabine might be more effective than either agent used alone in refractory/relapsed pediatric AML. A Phase 1 study of epigenetic priming prior to treatment with standard "7 + 3" induction therapy showed that DACOGEN could be given for 5 days prior to standard induction therapy.[35] Preclinical data using human pediatric primary AML explants suggest the sequence of DACOGEN followed by cytarabine would be effective in patients with relapsed or refractory disease.[30] The DACOGEN dosing regimen for this study is the same as that shown to be effective and approved for the treatment of adult (>65 years) patients with AML.[11] Because there are no expected differences in PK parameters for decitabine between children

and adults and children typically tolerate chemotherapy better than older adults this study was designed to quickly identify unexpected pediatric toxicities and provide a timely assessment of efficacy.

The purpose of this study is to examine the safety and efficacy of DACOGEN in sequential administration with cytarabine, which is the backbone of current standard combination treatments for relapsed/refractory pediatric AML. If the sequential treatment can be safely administered with a clinically interesting level of activity, then this study would provide the basis for further evaluation in this indication.

Phase 1:

The Phase 1 dose finding portion of the study will utilize a "rolling 6" design.[39] The rolling 6 design is a simple modification of the standard "3+3" design, and is consistent with the escalation rules and properties of the "3+3" design. The "rolling 6" aims to shorten the duration of pediatric Phase 1 studies by minimizing the time the study would be closed to accrual for toxicity monitoring while potentially speeding the completion of study by eliminating the need for inter-cohort study suspension of recruitment.

This method allows accrual of 2 to 6 subjects continuously onto a dose level based on the numbers of subjects who are currently enrolled and evaluable, without requiring that the DLT status of the subjects already assigned to the same dose level is known; hence reducing the number of subjects who would be refused study entry due to unavailability of open slots.

Use of the "rolling 6" design is justified on the basis that pediatric trials are typically conducted only after completion of extensive adult trials where much of the safety characteristics of the drug under study are known, as is the case for DACOGEN. The use of this design is intended to shorten the duration of the study and enroll subjects efficiently in situations in which there is prior information about the dose range to be evaluated.[42]

Phase 2

The Phase 2 portion of this study comprises at least 15 evaluable subjects and is aimed to provide initial efficacy and additional safety data of the sequential administration of DACOGEN and cytarabine.

Biomarker Collection

Acute myeloid leukemia, in common with many haematological malignancies, is a disease which is defined and characterized by particular gene signatures that could be both predictive of response to therapy and prognostic of outcome. Further gene mutation and gene expression profiling research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the biomarker component is to collect biological samples to allow for the identification of genetic and other biological factors that may influence the efficacy of DACOGEN and to identify additional genetic and biological factors associated with AML.

Biomarker samples in the form of peripheral blood and bone marrow aspirates will also be collected to evaluate the mechanism of action of DACOGEN or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to a drug. The goal of the biomarker analyses is to evaluate the

potential pharmacodynamics of DACOGEN and aid in evaluating the drug-clinical response relationship to decitabine + cytarabine.

Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

Biomarker analyses may be performed to assess pharmacodynamic effects across age groups if there is an adequate distribution of subjects across age categories. Additional analyses may be performed to explore potential predictive markers for response to decitabine + cytarabine treatment.

4. SUBJECT POPULATION

This is a Phase 1-2 pediatric study of a sequential combination of DACOGEN plus cytarabine in children with relapsed or refractory AML 1 month of age to less than 18 years old. Screening for eligible subjects will be performed within 14 days before administration of any study drug.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

1. Subject must be 1 month of age to <18 years of age at the screening visit.

2. Subject must have a histological diagnosis of AML according to the WHO classification

3. Criterion modified per Amendment INT-1:

   3.1. Subject must have AML which has relapsed or is refractory to standard of care and no curative therapy exists

   - Subjects in relapse must have at least 5% blasts in the bone marrow, with or without extramedullary disease and immunophenotypic confirmation of AML. Subjects who relapsed post- bone marrow transplant (BMT) are allowed, provided >3 months has elapsed since BMT and the subject does not have active graft-versus-host disease.
   - Subjects refractory to previous chemotherapy must have at least 20% blasts in the bone marrow

4. Subject must have a Karnofsky or Lansky score of at least 50

5. Subject must be recovered from acute toxicity of any prior treatment

6. Inclusion criterion has been modified:

   6.1 Criterion modified per Amendment INT-1

   6.2 Criterion modified per Amendment INT-2

   Subject must have adequate organ function, defined as:

   - Normal renal function defined as a creatinine clearance of at least 90 mL/min/1.73 m^2 as determined using the Schwartz equation.[37] Glomerular Filtration Rate (ml/min/1.73 m^2 = k*Height(cm)/serum creatinine (mg/dL) where k is a proportionality constant which varies with age and is a function of urinary creatinine excretion per unit of body size; k is 0.45 for children up to 12 months of age, 0.55 for older children and adolescent girls and 0.70 for adolescent boys (adolescent is referring to 12 to 18 years of age).
   - Alanine aminotransferase (ALT) ≤5 x upper limit of normal (ULN) and total bilirubin less than 1.5 x ULN. If ALT is transiently elevated and clearly related to recent prophylactic intrathecal treatment since start of screening but prior to the first dose of decitabine, it should be discussed with the sponsor's medical monitor whether the dose can be started or should be postponed.
   - Cardiac function must be normal, defined as shortening fraction of ≥29% by echocardiogram, or left ventricular ejection fraction (LVEF) >58%. Results obtained prior the screening period are acceptable provided no potentially cardiotoxic medication was administered between that evaluation and the first dose of decitabine (Cycle 1 Day 1).

7. Any female subject of childbearing potential must practice a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject).

   Note: If the childbearing potential changes after start of the study (eg, girl who is not heterosexually active becomes active, premenarchal girl experiences menarche) a girl must begin a highly effective method of birth control, as described above.

8. Female subjects of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-hCG) test at screening or a negative urine pregnancy test at Day 1 of Cycle 1

9. Criterion deleted per Amendment INT-1.

10. Criterion modified per Amendment INT-1:

    10.1. A male subject who is sexually active with a girl of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

11. The subject and his/her legally acceptable representatives (parent(s) or guardian(s)) must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

12. Each subject (or his/her legally acceptable representative per local regulations) must sign an informed consent/assent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. Assent may be required of children capable of understanding the nature of the study as described in Section 16.2.3, Informed Consent/assent.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

1. Subject has had prior treatment with DACOGEN or azacitidine (Vidaza).

2. Subject has acute promyelocytic leukemia (M3 subtype in the French-American-British [FAB] classification system).

3. Criterion modified per Amendment INT-1:

   3.1. Subject has central nervous system disease category 3 (CNS3), ie, more than 5 white blood cells per microliter and positive cytospin along with clinical symptoms and requiring intrathecal therapy.

4. Subject has AML associated with congenital syndromes such as Down syndrome, Fanconi anemia, Bloom syndrome, Kostmann syndrome or Diamond-Blackfan anemia, or bone marrow failure associated with inherited syndromes.

5. Criterion has been modified per Amendment INT-2:

   5.1 Subject has a white blood cell count greater than 40 x 10^9 cells/L

6. Subject has known allergies, hypersensitivity, or intolerance to DACOGEN or cytarabine or their excipients (see Investigator's Brochure for DACOGEN details, SmPC for cytarabine details).

7. Subject has contraindications to the use of cytarabine per local prescribing information or prior adverse reactions to cytarabine which would prevent further use.

8. Criterion modified per Amendment INT-1:

   8.1. Subject is currently enrolled in the treatment phase of an interventional investigational study.

9. Subject is a female who is pregnant (positive βHCG), or breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study drug. However, the period after which it becomes safe to become pregnant after the last dose of treatment is not known.

10. Subject is a male who plans to father a child while enrolled in this study or within 3 months after the last dose of study drug.

11. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, lack of recovery from surgery) or that could prevent, limit, or confound the protocol-specified assessments.

12. Subject has any social or medical condition that in the investigator's opinion renders the subject unfit for study participation.

13. Subject has a history of hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease.

14. Subject has a history of human immunodeficiency virus (HIV) antibody positive.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that they no longer meet all eligibility criteria, they should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. A female of childbearing potential must remain on a highly effective method of birth control (see inclusion criteria).

2. A male who is sexually active with a girl of childbearing potential must use a double-barrier method of birth control (ie, male condom, female diaphragm or cervical cap, or condom) and all boys must also not donate sperm during the study and for 3 months after receiving the last dose of study drug.

5. TREATMENT ALLOCATION

Randomization and blinding is not applicable for this study. All subjects will receive DACOGEN and cytarabine in the Phase 1 and Phase 2 portions of the study as indicated in Section 6: Dosage and Administration. After completing up to 4 cycles of the DACOGEN - cytarabine regimen, subjects who, in the opinion of the treating physician may benefit, can receive single agent DACOGEN at 20 mg/m^2 on Days 1 to 5 every 28 days for as long as such treatment is considered beneficial.

6. DOSAGE AND ADMINISTRATION

6.1. Materials and Supplies

6.1.1. DACOGEN

DACOGEN (decitabine) is supplied as a lyophilized powder for injection. It is supplied by Janssen R&D. The vials of DACOGEN must be stored according to the clinical trial label.

For more information with regard to the chemical properties of DACOGEN, see the IB.[11] For handling, storage, and preparation instructions, please refer to the Investigational Product instruction manual or equivalent.

6.1.2. Cytarabine

Cytarabine (cytosine arabinose) is supplied commercially by the investigational site. For more information consult the SmPC for cytarabine for the local country.

6.2. Drug Inventory and Dispensing

An initial supply of DACOGEN will be shipped to each site's pharmacy when all initiation documents, including Institutional review Board (IRB)/ethics committee (EC) approval and IRB/EC-approved Informed Consent/assent, have been received and reviewed by the sponsor or designee and occurs upon activation of the site via the Interactive Voice Response System/ Interactive Web Response System (IVRS/IWRS). Cytarabine will be purchased from commercial sources by each study site.

Supply of DACOGEN will be managed via the IVRS/IWRS. An accurate record of shipment and dispensing of the DACOGEN will be maintained by the Principal Investigator or his/her designee. These records will be available for inspection by Janssen R&D, their representatives, and the regulatory authorities of applicable counties at any time. A copy of the DACOGEN inventory will be provided to the sponsor at the conclusion of the study or as the record is completed.

Drug supplies for this study are to be used only in accordance with this protocol and under the supervision of the Principal Investigator. The Principal Investigator must ensure that any unused vials of DACOGEN be returned to Janssen R&D or destroyed as authorized by Janssen R&D. Periodically throughout and at the conclusion of the study, vials of DACOGEN will be inventoried by Janssen R&D or their designee.

The investigator and pharmacist of each site will be responsible for dispensing clinical supplies, for exercising accepted medical and pharmacy practices, and maintaining accurate records of receipt of vials of DACOGEN, including date(s) received and total number of vials received.

In addition, accurate records must be kept regarding when and how much of each study drug (DACOGEN and cytarabine) was dispensed to and used by each individual patient in the trial. Reasons for departure from the expected dispensing regimen must also be recorded. Study drug inventory will be verified at each monitoring visit throughout the study. A copy of the study drug inventory will be provided to the sponsor at the conclusion of the study or as the record is completed. At the completion of the study, unopened vials of DACOGEN will

be returned to the sponsor for destruction or alternatively disposed of as authorized by the sponsor.

6.3. Dosage and Administration

DACOGEN will be administered as a 1-hour IV infusion of 20 mg/m^2 once daily for 5 consecutive days on Days 1 to 5 of each 28 day cycle. Cytarabine will be administered as an IV infusion over 4 hours daily for 5 consecutive days (Day 8 to Day 12). The DACOGEN dose is considered the biologically active dose based on studies of DNA hypomethylation in adults and is far below (1/20th) the MTD for single-agent decitabine determined in children and adults.[1,20] The amounts of both agents are determined by body surface area calculations.

The dose should be recalculated if the subject's body surface area (BSA) changes by more than 10%. For subjects who are less than 1 year old, or have a body weight of less than 10 kg, the assigned doses of DACOGEN and cytarabine should be based on the subject's body weight. This conversion is calculated as dose described by BSA in mg/m^2 divided by 30 and multiplied by body weight (kg).

The MTD of cytarabine will be determined in the Phase 1 portion of the study. The starting dose of cytarabine will be 1 g/m^2 per day x 5 days and the second dose level will be 2 g/m^2 per day x 5 days. If the first dose level is not tolerated the study will stop since cytarabine 1 g/m^2 per day x 5 days is the lowest dose generally used in this setting. If the first dose level is tolerated but the second dose level exceeds the MTD, an intermediate dose level, 1.5 g/m^2 per day x 5 days will be evaluated.

In the Phase 1 portion, dose limiting toxicity (DLT) will be assessed for each subject who receives at least 1 cycle of the sequential DACOGEN - cytarabine treatment. Subjects will be enrolled into Phase 1 using a "rolling 6" design.[39] A minimum of 2 subjects and up to 6 subjects will be continuously enrolled at each dose level. Enrollment suspension for each dose level may occur only when 6 subjects have been enrolled.

Table 3 depicts the decision making algorithm for the determination of the appropriate dose level of cytarabine for the next enrolled subject, enrollment suspension, MTD determination, or study termination.

The algorithm counts only subjects who are evaluable or whose data are still pending, ie, subjects who are enrolled but are non-evaluable (do not complete Cycle 1 and do not develop DLT) are not counted. For each dose level, the algorithm starts when 2 subjects have been enrolled. The left portion (3 columns) of Table 3 indicates the current accrual and DLT status; and the right portion depicts the corresponding decisions to be made based on the current dose level. Since the algorithm depends on subjects' status that can change over time, subjects' status as current as possible prior to the next enrollment (or other decision making) should be obtained.

To use the algorithm, a combination of 3 key numbers should be gathered (left 3 columns of Table 3): (1) the total number of subjects who have been enrolled at the current dose level minus those who are non-evaluable; (2) the number of subjects who had DLTs; and (3) the number of subjects who have completed Cycle 1, are evaluable, and have no DLT. The

number of subjects whose data are still pending is not essential and hence is not shown in the table.

For example, if 4 subjects have been enrolled at the 2.0 g/m^2 per day dose level (none is non-evaluable), no DLT has been seen, 3 have completed Cycle 1 (this implies 1 subject with data pending); the 3-number combination in this case would be {4, 0, 3}. Then, shown in right part of the table (light gray shading), the next subject would receive the 2.0 g/m^2 dose. If 2 subjects have DLTs out of the 4 enrolled, the 3-number combination would be {4, 2, any}. In this case, shown in dark gray shading, the next subject would receive the 1.5 g/m^2 dose

Table 3: Dose Escalation and De-Escalation Algorithm for the "rolling 6" Design

Number of Subjects and DLT Status			Next Enrollment Dose Level (g/m^2 per day)		
Subjects Enrolled[a]	Subjects with DLT	Subjects without DLT[b]	Current Dose level 1.0 g/m^2 per day	Current Dose level 2.0 g/m^2 per day	Current Dose level 1.5 g/m^2 per day
2	0,1	0,1,2	1.0	2.0	1.5
	2	0	Stop[c]	1.5	MTD=1.0
3	0,1	0,1,2	1.0	2.0	1.5
	0	3	2.0	2.0	1.5
	≥2	Any	Stop[c]	1.5	MTD=1.0
4	0,1	0,1,2,3	1.0	2.0	1.5
	0	4	2.0	2.0	1.5
	≥2	Any	Stop[c]	1.5	MTD=1.0
5	0,1	0,1,2,3,4	1.0	2.0	1.5
	0	5	2.0	MTD	MTD
	≥2	Any	Stop[c]	1.5	MTD=1.0
6	0,1	0,1,2,3,4	Suspend	Suspend	Suspend
	0,1	5,6	2.0	MTD	MTD
	≥2	Any	Stop[c]	1.5	MTD=1.0

Note: This algorithm selects 1.0 g/m^2 as the MTD and stops the entire enrollment once 1.5 g/m^2 exceeds the MTD. Total number of evaluable subjects at dose level 1.0 g/m^2 can be as few as 3.

[a] Subjects complete Cycle 1 and evaluable for DLT, or with pending data, excluding non-evaluable subjects.

[b] Subjects complete Cycle 1 and evaluable for DLT.

[c] Dose level 1.0 g/m^2 exceeds MTD.

Up to 18 evaluable subjects may be enrolled if the intermediate cytarabine dose level (1.5 g/m^2 per day) is tested and all 3 dose levels recruit 6 subjects.

Subjects enrolled in the Phase 2 portion of the study will receive sequential administration of DACOGEN and cytarabine with the MTD of cytarabine, determined in Phase 1.

For subjects enrolled in either the Phase 1 or Phase 2 portion of the study, treatment may be repeated for up to 4 cycles with the sequential administration of DACOGEN followed by cytarabine. Subjects in Phase 1 can receive up to 4 cycles at their current dose level of cytarabine if an MTD for cytarabine has not been established. Once an MTD for cytarabine is declared, subjects who are receiving cytarabine at a dose other than the MTD for less than 4 cycles can receive the MTD dose of cytarabine for their remaining cycles as long as only 4 cycles total are administered. Subjects may continue to be treated with DACOGEN as monotherapy (20 mg/m^2 IV infusion over 1 hour for 5 consecutive days every 28 days) in the Continuation Phase as long as they are considered to derive benefit in the investigator's opinion. During this period subjects will be assessed for safety, concomitant therapies, and adverse events and disease assessment as clinically indicated.

6.3.1. Dose Delays

Cycles may be delayed up to 28 days to allow for recovery from toxicity. Subjects with bone marrow aplasia/hypoplasia (defined as overall marrow cellularity less than 25%) or absolute neutrophil count (ANC) <0.5 x 10^9/L or non-transfusion dependent platelet count <25 x 10^9/L should not start their next cycle until further hematopoietic recovery. The DACOGEN dose will be held constant but the cytarabine dose may be adjusted for toxicity.

7. TREATMENT COMPLIANCE

Study drugs will be administered as IV infusions by qualified study-site personnel and the details of each administration will be recorded in the electronic Case Report Form (eCRF; (including date, start and stop times of the IV infusion, and volume infused). Under these conditions treatment compliance is ensured.

8. PRESTUDY AND CONCOMITANT THERAPY

All prior therapies for AML must be recorded. CNS-directed intrathecal therapy administered within 30 days before the first dose of study drugs must be recorded.

Prophylactic intrathecal therapy and hydroxyurea are allowed until 1 day prior to Cycle 1 Day 1.

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study drug to 30 days after the last dose of study drug.

Concomitant therapies allowed under this protocol are:

- Packed red blood cell transfusion: transfusions may be given as clinically indicated
- Platelet transfusion: to be administered when platelets are <10,000/μL or according to institutional standards.
- Prophylactic antibiotics will be administered according to institutional standards.
- Management of febrile neutropenia should be in accordance with institutional standard:

Febrile neutropenia is defined as a body temperature of at least:

38.5°C on 1 occasion or 38°C on 2 occasions when the ANC is <1000/μL. Febrile patients are to be evaluated by physical exam, complete blood count (CBC) with differential, and blood culture. Patients with febrile neutropenia or suspected sepsis on the basis of physical exam are to be hospitalized for appropriate broad-spectrum antibiotic coverage, consistent with local pathogen sensitivities.

- Anti-emetics and other agents needed for supportive care may be given in accordance with institutional treatment standards
- Any other medications required for clinical management of the patient
- Other than the study agents, patients cannot receive other anticancer chemotherapy during this study.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies (eg, other anticancer medications) are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of the assessments applicable for this study before and during the Sequential Treatment period, the Continuation Phase for subjects electing to receive DACOGEN single-agent therapy, and the Follow-up period after the end of any study treatments.

All subjects will be followed from the first day of sequential therapy (Day 1 of Cycle 1) according to the assessment schedule outlined in the Time and Events Schedule regardless of whether the patient completes or discontinues sequential therapy (DACOGEN followed by cytarabine). Study assessments will be performed only after written informed consent/assent is obtained. Every effort should be made to keep subjects on the study schedule as planned from Study Day 1. At each visit, study assessments should be completed before the administration of the study drugs. Every effort should be made to conduct disease evaluations as per schedule; however, post-baseline disease evaluations may be conducted ±3 days from the scheduled visit date (based on Study Day 1), if necessary. At the following visit, the subject should return to the original planned schedule. Any missed visits, tests not performed, or examinations that are not conducted must be reported as such on the electronic case report form (eCRF).

Sample collections for biomarker and pharmacokinetic assessments should be kept as close to the specified times as possible. Other measurements may be done earlier than specified, if needed. Actual dates and times of the assessments must be recorded at minimum on the laboratory requisition forms. If required, serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

The total blood volume for the study is approximately 69 mL: 2 ml for cytogenetic assessment, 50 mL for safety and efficacy (including peripheral blood counts), 3.5 mL for PK, 6 mL for pharmacodynamic assessments, and 7.5 mL for biomarkers (Table 4).

Table 4: Volume of Blood to be Collected From Each Subject

Type of Sample[a,b]	Volume per Sample (mL)	No. of Samples per Subject	Total Volume of Blood (mL)[c]
Safety (including screening and post treatment assessments)			
- Hematology	2mL	18	36mL
- Serum chemistry[d]	2mL	7	14mL
Efficacy			
Pharmacokinetic samples	0.5mL	7	3.5mL
Pharmacodynamic (DNA methylation/ gene expression)	2mL	3	6mL
Biomarkers	2.5mL	3	7.5mL
Cytogenetics	2mL	1	2mL
Approximate Total			69mL

[a] Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
[b] Sample volumes will be adjusted according to standards for pediatric subjects
[c] Calculated as number of samples multiplied by amount of blood per sample.
[d] Serum chemistry includes serum β-hCG pregnancy test if urine pregnancy test is not performed at the site.
Note: An indwelling intravenous cannula may be used for blood sample collection. If a mandrin (obturator) is used, blood loss due to discard is not expected.

9.1.2. Screening Phase

The signed ICF/assent must be obtained before any study-specific procedures are performed. The Screening Phase begins when the first study-specific screening assessment is conducted. During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed. Screening procedures will be performed up to 14 days before Cycle 1 Day 1; however, results of tests such as radiologic tests, bone marrow collection for morphology, cytogenetics, and either immunohistochemistry or immunofluorescence performed up to 28 days before Cycle 1 Day 1 as routine work-up for the subject's disease can be used. Cardiac function must be normal, defined as shortening fraction of ≥29% by echocardiogram or LVEF >58%. Results obtained prior the screening period are acceptable provided no potentially cardiotoxic therapy was provided between that evaluation and the first dose of decitabine (Cycle 1 day 1). A negative pregnancy test for females of childbearing potential must be documented within 7 days before the Cycle 1 Day 1 dosing. If a pregnancy test result is more than 7 days old at Cycle 1 Day 1, then the test must be repeated locally and documented.

9.1.3. Sequential Treatment Phase

Subjects are to receive sequential treatment in either the Phase 1 or Phase 2 portion of the study. Details of the procedures performed during the Treatment Phase are specified in the Time and Events Schedule. The Sequential Treatment Phase (DACOGEN – cytarabine) begins on Cycle 1 Day 1 and continues until the completion of 4 cycles of treatment, provided there is no evidence of disease progression, unacceptable toxicity, or for the other reasons outlined in Section 10.2.

Subjects will be closely monitored for adverse events, laboratory abnormalities, and clinical response. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. The next cycle can be started per investigator decision as long as the subject has recovered from acute toxicity and does not meet any of the discontinuation

criteria (Section 10.2). If disease progression is diagnosed, then the subject will discontinue the study treatment, complete the End of Sequential Treatment Visit, End of Treatment Visit, and enter the Follow-up Phase.

9.1.4. End of Sequential Treatment Visit

Subjects will be treated for a maximum of 4 cycles with DACOGEN - cytarabine sequential therapy. Once a patient completes or discontinues the sequential treatment portion of the study they will have the End of Sequential Treatment Visit at the end of the last cycle of sequential therapy.

9.1.5. Continuation Phase

After completing up to 4 cycles of sequential DACOGEN - cytarabine treatment or discontinuing sequential treatment for reasons other than progressive disease, subjects who, in the opinion of the treating physician are deriving benefit from DACOGEN treatment can continue to receive single agent DACOGEN at 20 mg/m^2 IV infusion over 1 hour on Days 1-5 every 28 days in the study continuation phase for as long as such treatment is considered beneficial. Treatment may continue at the investigators discretion until the patient is either eligible for transplant, has progressive disease, or experiences unacceptable toxicity.

Subjects who start single agent DACOGEN will be followed for safety and efficacy until the treatment ends. In the event subjects continue to derive benefit at study end, DACOGEN will continue to be supplied by the Company.

9.1.6. End of Treatment Visit

Unless a subject withdraws consent from study participation, an End of Treatment Visit is to be scheduled 30 days ± 5 days after the last dose of any study drug. Every effort should be made to conduct the End of Treatment Visit before the subject starts any subsequent therapy. If a subject is unable to return to the site for the End of Treatment Visit, then the subject should be contacted to collect adverse events that occurred within 30 days after the last dose of any study drug. Additional information on reporting of adverse events can be found in Section 12. If the End of Sequential Treatment Visit is within 3 days of the End of Treatment Visit Hematology and Chemistry lab assessments do not need to be repeated.

9.1.7. Follow-up Phase

The Follow-up Phase will begin after the completion of the End of Treatment Visit. Follow-up assessments will be performed as specified in the Time and Events Schedule. Follow up visits will be performed every 3 months during the Follow-up Phase and will record disease progression, subsequent anticancer treatment including stem cell transplant, survival status, and late-occurring, potentially study-drug-related adverse events.

If the information is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented on the eCRF. Follow-up of subject data will continue for a maximum of 3 years from the enrollment of the last subject or when 80% of the patients are deceased, whichever comes first.

Investigators may contact the subject to obtain follow-up information to determine the subject's safety or survival status (refer to Section 16.2.3, Informed Consent).

9.2. Efficacy

9.2.1. Evaluations

Efficacy evaluations will be performed according to the Time and Events Schedule until transplant, disease progression, withdrawal from the study, or death. Evaluations are to be performed ±3 days of the scheduled evaluation date (within +8 days and up to Day 42 in the case of end of cycle evaluations). If treatment has been delayed for any reason, then the disease evaluations must be performed according to appropriate point in the treatment cycle, resulting from changes to the dosing regimen. Response will be assessed using the IWG criteria as published in The Journal of Clinical Oncology, 21: 4642-4642 2003 and erratum 22: 576, 2004.[6] Response will be evaluated prior to the start of each cycle.

Hematology including peripheral blast counts will be performed during screening, at Day 1, Day 5 (first cycle only), Day 8, Day 22 (first cycle only), and Day 28 or later if the next cycle is delayed but within 8 days of the start of the next cycle.

Bone Marrow Examination

Bone marrow aspirate or biopsy will be performed and examined by the local laboratory at screening for clinical staging (morphology is required), at the end of Cycle 1, at the end of Cycle 2 if the subject has not attained a CR in Cycle 1, at the End of Sequential Treatment Visit, and at any time disease progression is suspected. Cytogenetic evaluations will be performed at screening. If tests such as immunophenotyping and/or cytochemical evaluations have been done for standard medical care prior or within screening period, the data will be collected in the eCRF. During the Continuation Phase, bone marrow sampling and assessments will be done as clinically indicated.

For Phase 1, bone marrow aspirates at end of Cycle 1 should be obtained no later than Day 42 in order to determine a potential DLT.

Remission and Disease Progression/Relapse

The assessment of a response (CR or CRi), may be made only when laboratory findings meet specific criteria as defined by IWG.[6] The timing of bone marrow assessments for efficacy endpoints will be driven by peripheral blast counts. Clinical judgment based on blood cell count recovery will dictate the exact time in each cycle when bone marrow aspirates should be taken.

Some patients may develop a relapse that leads to death quickly without having the possibility to evaluate formally the relapse of disease. Efforts should be made to obtain an autopsy report in such patients.

The dates of CR, CRi, PR, progressive disease, or any subsequent disease relapse after a response should be recorded. This should be based on the acceptable laboratory evidence from a bone marrow aspirate.

Details of the IWG criteria are given below:

Complete Remission

For the following 2 CR categories, extramedullary leukemia, such as CNS or soft tissue involvement, must be absent. There is no stated duration of response required for a subject to be classified as a complete responder.

- **Morphologic Complete Remission (CR)**

  Per the IWG criteria, CR is defined as morphologic leukemia-free state, with less than 5% blasts in aspirate sample with marrow spicules and with a count of ≥200 nucleated cells (there should be no blasts with Auer rods or any persistence of extramedullary disease), **plus** ANC >1,000/µL platelet count of >100,000/µL and subject must be independent of transfusions for a minimum of 1 week before each marrow assessment. No duration of response is required for CR.

- **Morphologic Complete Remission with incomplete blood count recovery (CRi)**

  Per the IWG criteria, CRi is defined as morphologic CR with residual neutropenia (<1,000/µL) or thrombocytopenia <100,000/µL). No stated duration of response is required for CRi.

Partial Remission (PR)

Per the IWG criteria, PR is defined as all the same hematologic values of a CR, but with a decrease of ≥50% of the percentage of blasts to 5% to 25% in the bone marrow aspirate. Therefore, if the pretreatment bone marrow blast percentage was 50% to 100%, the percentage of blasts must decrease to a value between 5% and 25%; if the pretreatment blast percentage was 20% to less than 49%, they must decrease by at least half to a value of more than 5%. A value of ≤5% blasts may also be considered a PR if Auer rods are present. There is no stated duration of response required for PR.

Stable Disease (SD)

A subject who has no CR/CRi/PR nor has progressive disease for a period of at least 2 months should be considered stable disease (SD).

Progressive Disease

Progressive disease is defined as:

First Cycle: Determination of progressive disease will be based on peripheral blood (PB) count, evidence of new extramedullary disease and/or the clinical judgment of the investigator. If the blast counts in PB increases by >50% over the pre-treatment value during the first cycle, the subject will be considered as progressive disease if a bone marrow (BM) assessment was not performed. If BM assessment has been performed in first cycle or before the start of second cycle, then a >25% increase in the blasts count from baseline on BM aspirate is considered progressive disease.

During the subsequent cycles, progressive disease will be defined as >50% increase in peripheral blast count from baseline, >25% increase in the blast count from baseline on BM aspirate, or clinical evidence of new extramedullary disease or the clinical judgment of the investigator. Responses for patients who complete 3 or more cycles and never had a post-baseline bone marrow evaluation will be determined based on the clinical judgment of the investigator.

9.2.2. Endpoints

Primary Endpoints:

Phase 1

Dose Limiting Toxicity (DLT) for Cytarabine

For the Phase 1 portion of the study the primary endpoint will be DLT in the determination of the MTD (up to 2 g/m^2 per day) of cytarabine given on Days 8 to 12 following the administration of DACOGEN at 20 mg/m^2 on Days 1 to 5. DLTs are defined as the following

- Hematological DLT will be defined as failure to recover to an absolute neutrophil count (ANC) of 0.5 x 10^9/L (common terminology criteria for adverse events [CTCAE] Grade 3) and non-transfusion dependent platelet count of 25 x 10^9/L (CTCAE Grade 3) due to documented bone marrow aplasia/hypoplasia (malignant infiltration or other cause excluded), by Day 42. Bone marrow aplasia/hypoplasia is defined as overall marrow cellularity less than 25%.
- Non-hematological DLT is defined as: any Grade ≥3 toxicity possibly, probably or definitely related to study drug that persists for >5 days; any Grade 2 toxicity that persists for >7 days and that is intolerable to the patient.

The following events are more likely disease-related and, therefore, not considered DLTs:

- Grade 3 or 4 disseminated intravascular coagulation
- Grade 3 tumor lysis syndrome; grade 3 or 4 fever or grade 3 catheter-related infection, febrile neutropenia, infection, infection with unknown neutrophil count, and infection without neutropenia
- Grade 3 or 4 hypokalemia, hypomagnesemia, hyponatremia, or hypophosphatemia that is related to AML or administration of antifungal medications and is corrected with IV or oral supplementation.

Subjects who do not complete one treatment cycle and do not develop DLT will not be considered evaluable for DLT.

Decitabine PK parameters including C_{max}, AUC, t_{max}, and Cl will be determined from blood sampling on Day 5 of Cycle 1 and are a primary endpoint for the Phase 1 portion of the study.

Phase 2

Complete Response + Complete Response with incomplete recovery rate

In the Phase 2 portion of this study the primary end point will be the CR +CRi rate as determined using IWG criteria. The response status of each patient will be determined prior to each cycle of DACOGEN + cytarabine after the first cycle. The best response up to 4 cycles of DACOGEN + cytarabine for each subject will be used to determine the rate of CR + CRi.

To be evaluable, subjects must complete at least 2 cycles of the sequential retreatment and have at least 1 post baseline disease assessment unless disease progression or response (CR, CRi, or PR) occur prior to the planned disease assessment but after Cycle 1 treatment (ie, after Day 13 of Cycle 1).

Secondary Endpoints

- Safety profile of DACOGEN 20 mg/m^2 per day on Days 1-5 followed by cytarabine Days 8-12 for up to 4 cycles of therapy.
- Duration of CR + CRi
- Overall response (CR + CRi + PR)
- Event-free survival (EFS), defined as the time from first dose of study drug to relapse from CR, death, or second malignancy for subjects who achieve CR; subjects who do not achieve CR will be considered to have an event on the day of the first dose of study drug. Other alternative EFS definitions may be considered.
- Overall survival
- To determine the PK profile of DACOGEN in children with AML

Other Secondary Endpoints

- To explore pharmacodynamic effects of DACOGEN with respect to DNA hypomethylation status and gene expression
- To explore predictive markers for response to DACOGEN.
- Levels of DACOGEN in the CSF if samples are collected as part of other required medical care.

9.2.3. Pharmacokinetics Evaluations

Serial whole blood samples (0.5 mL each) for PK will be obtained on Day 5 of Cycle 1 as indicated in the Time and Events Schedule for determination of decitabine plasma concentrations. Blood samples for pharmacokinetic analyses should not be collected through the same line through which decitabine is infused. Pharmacokinetics samples can be taken via a central line if the decitabine infusion is given peripherally. If attempts to place a peripheral line are unsuccessful, and decitabine is given through a single lumen central line, consider to only collect pre-infusion and post-infusion PK samples. The exact dates and times of blood sample collection must be recorded at minimum on the laboratory requisition forms.

In subjects whose course of routine treatment includes sampling of CSF, a portion of that sample may be assessed for decitabine drug levels.

An interim PK analysis will be performed after the completion of Phase 1 PK assessments. Based on the results of the interim PK analysis of Phase 1, the collection timepoints of PK samples may be optimized and if possible reduced for the Phase 2 portion of the study.

9.2.4. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of decitabine using a validated, specific, and sensitive liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method under the supervision of the sponsor's Bioanalytical Laboratory Department of Bioanalysis.

PK sample collection, processing, storage, and shipping instructions for these PK blood samples are presented in the PK lab manual provided by the sponsor or sponsor's representative.

If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method.

9.2.5. Pharmacokinetic Parameters

PK analysis will be the responsibility of the Sponsor in accordance with the sponsor's current Clinical Pharmacokinetics Guideline. The following PK parameters for decitabine will be calculated on Day 5 of Cycle 1 by non-compartmental methods using WinNonlin Version 5.0 or higher:

C_{max}	maximum plasma concentration
t_{max}	time to reach the maximum plasma concentration
AUC_{last}	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC_{τ}	area under the plasma concentration-time curve from time 0 to 24 hr
$t_{1/2, \lambda}$	elimination half-life associated with the terminal slope (λ_z) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$
λ_z	first-order rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve
CL	total clearance of drug after IV administration, calculated as: $dose/AUC_{\tau}$
VD_{ss}	volume of distribution at steady state, calculated as λ_z /CL

Actual blood sampling times relative to study medication administration will be used for the analysis. Additional PK parameters may be determined as appropriate.

Cytarabine PK parameters will not be evaluated. They are already well described in this population at the doses planned. Since decitabine has a terminal half-life of 0.51 ± 0.31 hour (DACOGEN package insert) and two full days will pass from the last dose of decitabine to the first of cytarabine, no drug-drug interaction is expected.

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, pharmacokinetic parameters and exposure information of decitabine will be derived using population pharmacokinetic modeling. Baseline covariates (eg, body weight, age, sex, creatinine clearance, race) may be included in the model, if relevant.

9.3. Pharmacokinetic/Pharmacodynamic Evaluations

Decitabine plasma concentration-time models data will also be analyzed using a population PK approach (non-linear mixed effect models) to establish decitabine PK parameters (eg, clearance and volume of distribution). The population PK model proposed for the adult population will be updated with the data obtained in this patient population. Data from this study may be combined with data from other studies to perform the population PK analysis.

Analyses comparing PK parameters of C_{max} and AUC with PD endpoints of DNA methylation and gene expression profiling may be undertaken to explore any potential relationships.

9.4. Biomarkers

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and may be deferred or not performed if, during or at the end of the trial, it becomes clear that the analysis will have no scientific value or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event that the trial is terminated early or shows poor clinical efficacy, completion of biomarker assessments will be based on justification and intended utility of the data. Biomarker sample collections will be prioritized in the manner specified in Section 9.6 in the event total blood volumes exceeds the EMA recommendations for pediatric trial related blood loss. Biomarker samples will not be stored for future research.

9.4.1. Pharmacodynamic Evaluations

DNA methylation and gene expression will be evaluated as potential pharmacodynamic biomarkers of the mechanism of action for DACOGEN and as response markers for treatment by the sequential administration of DACOGEN and cytarabine. This data will also be used to show biological activity across all ages enrolled in the study. Whole blood and/or bone marrow aspirates will be collected before study drug administration and according to the time and events schedule.

9.4.2. Gene Expression Profiling

Gene expression profiling (GEP) may be evaluated in RNA for gene signatures predictive of response to DACOGEN. The expression of single genes such as estrogen receptor and $p15^{INK4B}$ may be examined in relation to response using RTqPCR.[4] Whole blood and/or bone marrow aspirates will be collected before study drug administration and according to the time and events schedule.

9.4.3. Gene Methylation Profiling

Gene methylation profiling will be evaluated in DNA as a predictor of response to treatment by the sequential administration of DACOGEN and cytarabine. The following genes will be highlighted for determination of efficacy: CDH1, CDH13, ER, NR4A3, NPM2, OLIG2, $p15^{INK4B}$, PGRA, PGRB, RIL.[38] Additional genes may be analyzed or global profiling may be applied as necessary. Whole blood and/or bone marrow aspirates will be collected before study drug administration and according to the time and events schedule.

9.4.4. Gene Mutation Profiling

Gene mutations in DNMT3a and NPM1[27] among others plus other genetic mutations relating to drug response or disease, such as FLT3, IDH1, IDH2, TET2 and CEBPA, MLL-PTD, c-KIT, WT1, PTPN11[10] will be evaluated for prediction of response to treatment by the sequential administration of DACOGEN and cytarabine in DNA obtained from whole blood and/or bone marrow aspirate. Whole blood and/or bone marrow aspirates will be collected before study drug administration and according to the time and events schedule.

9.4.5. MicroRNA Analysis

miR29b may be evaluated for prediction of response to treatment by the sequential administration of DACOGEN and cytarabine in microRNA obtained from whole blood and/or bone marrow aspirate.[5]

9.5. Safety Evaluations

The evaluation period for safety will start from the time a signed consent/assent is provided. Toxicity/safety will be determined using National Cancer Institute common terminology criteria for adverse events (NCI-CTCAE) version 4.0.

The primary expected toxicity of cytarabine is severe myelosuppression. In addition rare cases of hypersensitivity and anaphylaxis have been reported after cytarabine dosing as well as "sudden respiratory arrest syndrome" occurring 6 to 12 hours after dosing and tumor lysis syndrome.

In addition to myelosuppression, administration of DACOGEN can cause peripheral edema, pallor, cardiac murmur and hypotension. Fever, fatigue, headache, lethargy and other CNS symptoms may occur. Cough, dyspnea, pneumonia and pharyngitis may be seen as well as mucositis and other side effects associated with myelosuppression and cellular cytotoxicity.

For the purposes of DLT evaluation, Cycle 1 will last until the start of Cycle 2, unless there is no recovery from toxicity within the specified time.

During the conduct of Phase 1 the SET will evaluate the tolerability of the combination until such times as a MTD for cytarabine can be agreed upon. Details regarding the SET are provided in Section 11.9.

During Phase 1, blood counts are to be monitored, but hematological parameters are not used to determine the MTD (ie, low blood counts per se are not considered to be dose-limiting toxicities or serious adverse events) because peripheral blood counts and bone marrow function are compromised in patients with relapsed leukemia. Hematological toxicity will only be assessed in responding patients who have grade 4 neutropenia ($<0.5 \times 10^9$/L) or grade 4 thrombocytopenia ($<25 \times 10^9$/L) due to a hypoplastic marrow at Day 42, in the absence of leukaemia.

During Phase 2 only myelosuppression events that are considered life threatening or result in an admission to hospital would be considered as serious adverse events.

Safety will be measured by adverse events, laboratory test results, vital sign measurements, physical examination findings, and assessment of performance status. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached. The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule.

Any of the safety monitoring assessments may be performed more frequently, and adverse events should be evaluated by the investigator according to standard practice, and if clinically indicated.

Adverse Events

Adverse events (with the exception of disease progression) will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) or by the medical staff from the time of the signed and dated ICF until 30 days following the last dose of any study drug. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents. The analysis of bone marrow samples will be performed locally and evaluated by the investigator.

The following tests will be performed by the local laboratory unless otherwise indicated:

- Hematology Panel
  - Hemoglobin
  - platelet count
  - white blood cell (WBC) count
  - absolute neutrophil count (ANC)
  - peripheral blast count

- Serum Chemistry Panel
  - Sodium
  - Potassium
  - Creatinine
  - aspartate aminotransferase (AST)
  - alanine aminotransferase (ALT)
  - total bilirubin
  - serum uric acid

- Urine or serum pregnancy testing for females of childbearing potential at screening is required and during the study when clinically indicated.

Vital Signs: (pulse, temperature, and blood pressure) will be performed at screening and as needed during the study.

Physical Examination: A complete physical examination will be performed during the Screening Phase. Thereafter, only a symptom directed physical examination is required. Abnormalities will be recorded in the appropriate section of the eCRF.

Karnofsky/Lansky Performance Status Score: Karnofsky/Lansky Performance Status (see) will be used to evaluate the effect of the disease status on the activities of daily living, and will be performed at the times specified in the Time and Events Schedule.

Lansky Performance Status:[26]

Rating	Description
100	fully active, normal
90	minor restrictions with strenuous physical activity
80	active, but gets tired more quickly
70	both greater restriction of, and less time spent in, active play
60	up and around, but minimal active play; keeps busy with quieter activities
50	lying around much of the day, but gets dressed; no active play; participates in all quiet play and activities
40	mostly in bed; participates in quiet activities
30	stuck in bed; needs help even for quiet play
20	often sleeping; play is entirely limited to very passive activities
10	does not play nor get out of bed
0	unresponsive

Karnofsky/ Performance Status:[23,36]

Condition	Performance status %	Comments
Able to carry on normal activity and to work. No special care needed.	100	Normal. No complaints. No evidence of disease.
	90	Able to carry on normal activity. Minor signs or symptoms of disease.
	80	Normal activity with effort. Some signs or symptoms of disease.
Unable to work. Able to live at home and care for most personal needs. A varying degree of assistance is needed.	70	Cares for self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled. Requires special care and assistance.
	30	Severely disabled. Hospital admission is indicated although death is not imminent.
	20	Hospitalization necessary. Very sick, active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead.

9.6. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (USP) (or equivalent) or sodium heparin of 10 U/mL as per local practice and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected.

Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of

samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Any volume of blood collected must be consistent the recommendations of the European Medicines Agency (EMA) for study related blood loss. In pediatric populations this should be no more than 3% of the total blood volume during a four week period and not more than 1% of total blood volume at a single time point. At a total blood volume estimated at 80 to 90 mL/kg body weight this equals 2.4 to 2.7 mL of blood per kilogram of body weight every four weeks or 0.8 to 0.9 mL per kilogram at any one time.

It is the responsibility of the investigator to comply with these guidelines and to prioritize study blood collection as follows:

1. Safety laboratory studies (hematology and serum chemistry) that are trial related and not part of routine care
2. Pharmacokinetic samples
3. Samples for DNA methylation and DNA mutation.
4. Samples for gene expression profiling and microRNA analysis.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if he or she has completed the follow-up phase, has died before the end of the study, has been lost to follow up, or has withdrawn consent for study participation before the end of the study.

10.2. Discontinuation of Study Treatment (Sequential DACOGEN - cytarabine)

If a subject's study treatment must be discontinued, the End of Sequential Treatment Visit should be performed however, this will not result in automatic withdrawal of the subject from the study. The subject may, at the discretion of the investigator, receive single agent DACOGEN in the Continuation Phase (see Section 9.1.5), otherwise the subject will enter the Follow-up Phase of the study. The End of Sequential Treatment/End of Treatment Visit and Follow-up visit assessments should be performed as specified in the Time and Events Schedule.

A subject's study treatment should be discontinued if:

- The subject experiences a DLT in the Phase 1 portion of the study
- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject has progressive disease by IWG criteria
- The subject is non-compliant with regard to treatment visits
- The subject has sufficient clinical response, in the opinion of the investigator, to be eligible for transplant

- The subject starts another treatment regimen for AML
- The subject is unable to adhere to the study visit schedule or comply with protocol requirements
- The subject or subject's legal representative, parent, or guardian withdraws consent/assent for study treatment.

10.3. Withdrawal from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent/assent by the subject or the subject's legal representative, parent, or guardian.
- Sponsor terminates the study

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject.

If a subject withdraws from the study the research samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent/assent for the research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

11.1. Subject Information

The safety population includes subjects who have signed the ICF and have received at least 1 dose of any study drug. The efficacy population is the subset of the safety population consisting subjects who are evaluable for disease response. Where appropriate, summaries (demographic, baseline characteristics, efficacy, and safety) will be presented for Phase 1 part of the data, Phase 2 part of the data, and data of the 2 phases combined.

11.2. Sample Size Determination

The Phase 1 portion of the study will enroll up to 12 evaluable subjects (18 if the intermediate cytarabine dose is used), depending on when the MTD is determined. The Phase 2 portion of the study will enroll at least 15 evaluable subjects including those who received the MTD of cytarabine for up to 4 cycles in Phase 1 portion of the study and are evaluable.

The estimated numbers of subjects are 15 (20 if the interim dose is tested) for Phase 1, and 17 for Phase 2 (including those who received the MTD of cytarabine in Phase 1) allowing for those who are not evaluable.

11.3. Phase 1 Analysis

Subjects in the Phase 1 portion will be assessed for toxicity (DLT) to determine the recommended dose of cytarabine for the Phase 2 study.

11.4. Efficacy Analyses

Criteria

Primary Endpoint

The primary efficacy endpoint is the response rate of CR + CRi for evaluable subjects from the Phase 2 part of the study. The best response observed at any time point during the first 4 cycles of study treatment will be used.

Best response of CR + CRi for subjects from the Phase 1 part of the study, and from Phase 1 and Phase 2 parts combined will also be summarized.

The aim of the statistical analysis of the initial efficacy data is to assist decision making for further clinical development of DACOGEN sequential therapy. Such a decision will be in consultation with regulatory authorities, and will depend primarily on the totality of the data from this and other studies, available treatment options for pediatric AML patients at the time, and interest of co-operative study groups.

The sequential therapy is considered not to have a clinically interesting activity if the underlying response rate (CR + CRi) is ≤20%, and is considered to have a clinically interesting activity if the underlying response rate is ≥35%. Because of the small sample size (15 subjects), only descriptive statistics, ie, the observed response rate of CR + CRi and the 95% confidence interval (CI), will be provided without any hypothesis testing. Also, due to the small sample size, the observed response rate will have much variability. With these considerations, descriptive statistical analyses will focus on 2 assessments that are considered adequate and reasonable in the context of small sample sizes.

The first analysis is to use the lower boundary of the 95% CI to assess if an underlying response rate that is much smaller than 20% can be ruled out. For instance (Table 5), with a total of 15 subjects, to rule out an underlying response rate of 5%, there should be at least 4 responders, and to rule out an underlying response rate of 3%, there should be at least 3 responders.

The second statistical assessment to assist in decision making is the “false positive” and “false negative” error rates. This assessment estimates the probability of chance findings with the given sample size. Suppose a “yes” or “no” answer is sought in terms of whether the outcome, say x CR + CRi responders out of the 15 subjects, favors a continuation of the clinical program. The “false positive” error rate for a “yes” answer is the probability of observing ≥x responders when the underlying response rate is 20%; and the “false negative” error for a “no” answer is the probability of observing ≤x responders when the underlying

response rate is 35%. Table 5 illustrates the false positive and false negative error rates depending on the number of responders. For instance, if only 2 or 3 subjects have responded, the "false positive" error rate for a "yes" answer is very high (83% or 60%) indicating a "yes" is likely an incorrect answer, while the "false negative" error rate for a "no" answer is low (6% or 17%) indicating a "no" is likely a correct answer.

Table 5: Statistical Assessments of Response of CR + CRi (N=15)

Number of Responders	Response Rate (%)	Exact 95% CI (%)[a]	False Positive Error (%)[b]	False Negative Error (%)[c]
1	6.7	(0.2, 31.9)	96.5	1.4
2	13.3	(1.7, 40.5)	83.3	6.2
3	20.0	(4.3, 48.1)	60.2	17.3
4	26.7	(7.8, 55.1)	35.2	35.2
5	33.3	(11.8, 61.6)	16.4	56.4
6	40.0	(16.3, 67.7)	6.1	75.5
7	46.7	(21.3, 73.4)	1.8	88.7

[a] Based on Clopper-Pearson Exact Interval
[b] Probability of observing this or greater number of responders if the underlying response rate is 20%.
[c] Probability of observing this or fewer number of responders if the underlying response rate is 35%.

Major Secondary Endpoints

Duration of CR + CRi, overall response (CR + CRi + PR) rate, event-free survival, and overall survival will be summarized. These summaries are also based on data of the Phase 2 part of the study. Where appropriate, these summaries will be performed on data from the Phase 1 part of the study and Phase 1 and Phase 2 parts combined. The start time for EFS and OS determination is the date of the first dose of study drug.

11.5. Pharmacokinetic Analyses

Population PK analysis of plasma concentration-time data of decitabine will be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (demographics, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for decitabine and included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date, and may be included in a population PK re-analysis when they become available after database lock.

Data will be listed for all subjects with available plasma concentrations per treatment group. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study drug; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the study report.

For each treatment group, descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated for all individual derived PK parameters including exposure information of decitabine.

All plasma concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations or SAS dataset. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

Descriptive statistics will be used to summarize decitabine serum concentrations at each sampling time point and PK parameters of decitabine: C_{min} and C_{max}. Other PK parameters, including but not limited to $AUC_{(t1-t2)}$, $t_{1/2}$, CL, and V, when available, will also be summarized.

11.6. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between decitabine plasma concentrations and/or metrics of systemic exposure (C_{max}, AUC) with markers of pharmacological activities (DNA methylation status, gene expression profiles) will be explored using suitable structural models and non-linear mixed effect regression techniques.

11.7. Biomarker Analyses

Biomarker analyses will be performed and stratified by clinical covariates or molecular subgroups using appropriate statistical methods. When too few data are available for statistical analyses, data will be summarized with descriptive statistics and/or visualized.

Pharmacodynamic biomarker results from Phase 1 and 2 will be summarized with descriptive statistics and/or visualized for each dose level. Changes in the values of individual biomarkers from baseline to selected time points will be summarized by dose cohort.

Correlation of baseline values or changes in biomarker values with response or time-to-event endpoints will identify responsive (or resistant) subgroups of patients as well as genes and pathways affected by DACOGEN treatment.

Planned biomarker analyses are dependent upon the availability of appropriate biomarker assays and may be deferred if emerging study data show no likelihood of providing useful scientific information.

Results of biomarker analyses will be presented in a separate report.

11.8. Safety Analyses

If appropriate, safety data will be summarized for the Phase 1 part and Phase 2 part of the study separately, and for all the 2 parts combined.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.1 or higher. All reported adverse events with onset during the treatment phase

(ie, treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Parameters with predefined National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables.

Cardiac Monitoring

An assessment of shortening fraction and/or left ventricular ejection fraction (LVEF) will be assessed during screening by echocardiogram.

$$\text{LVEF} = \frac{\text{left ventricular (LV) diastolic volume} - \text{LV systolic volume}}{\text{LV systolic volume}}$$

$$\text{Shortening Fraction} = \frac{\text{LV end diastolic diameter} - \text{LV end systolic diameter}}{\text{LV end diastolic diameter}}$$

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

Physical Examination

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

11.9. Study Evaluation Team

A Study Evaluation Team (SET) will be established to review the safety data of the Phase 1 portion of the study to determine dose escalation, dose de-escalation, and the MTD of cytarabine.

The SET consists of the sponsor's statistician and clinician (one of whom will chair the committee) and other members as needed, eg, clinical pharmacologist, safety physician. The SET will also include the lead investigator or designee from each country where the study is being conducted. The SET will convene regularly during the Phase 1 portion of this study to assess DLTs, determine dose escalation or de-escalation, and whether a MTD has been reached for cytarabine under these study conditions. The SET may convene at additional times for data review or any safety-related issues including during Phase 2. Any SET member has the right to request a SET meeting. A medical consultant may be asked to participate in the SET if deemed necessary in the interest of patient safety, upon request from the Sponsor or the investigator in preparation for SET meetings. Decisions on dose escalations or de-escalations, changes in the timing of PK or PD sampling, or other study conduct recommendations, will be made by the SET and documented.

All decisions made by the SET (eg, dose escalation/de-escalation, modification of the administration schedule or regimen) will be documented in a SET decision document and distributed to investigators. The IRB will be notified before implementation of any SET decision, if required. This document template will be provided in the sponsor's instruction manual and retained in the study master file and in the study center's files.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.2.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For DACOGEN, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For cytarabine, with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the SmPC.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study drug
- Unexpected therapeutic or clinical benefit from use of a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

12.2. Procedures

12.2.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study drug. Serious adverse events, including those spontaneously reported to the investigator

within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.2.1, All Adverse Events, for time of last adverse event recording).

12.2.2. Serious Adverse Events

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drugs and the event (eg, death from anaphylaxis), then the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Administration of study drugs
- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)

- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.

12.2.3. Disease Progression

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1, Adverse Event Definitions and Classifications).

12.2.4. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the study drug may have an effect on sperm, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event, using the appropriate pregnancy notification form.

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

12.3. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.2.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The DACOGEN supplied for this study is the commercially approved product that will be relabeled in local languages as “Clinical Supply Only”. DACOGEN (decitabine) for Injection is a white to almost white sterile lyophilized powder supplied in a single-use 20 ml vial containing 50 mg decitabine. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

Cytarabine for this study will be the commercially approved product and locally sourced by each investigator site. Refer to the SmPC of cytarabine for product details.

14.2. Packaging

DACOGEN will be packaged in individual subject kits. Each kit will consist of 5 20 mL vials containing 50 mgs of lyophilized decitabine.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study drug must be stored according to the clinical trial label.

Refer to the pharmacy manual/study site Investigational Product instruction Manual or equivalent for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drugs received at the site is inventoried and accounted for throughout the study. The study drugs administered to the subject must be documented on the drug accountability form. All study drugs will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes, vials, and infusion materials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator Brochure for DACOGEN; SmPC for cytarabine
- Pharmacy manual/study site investigational product manual
- Laboratory manual
- NCI-CTCAE Version [4.0]
- IVRS/IWRS Manual
- eDC Manual
- Sample ICF
- Lab kits

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent/assent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent/assent voluntarily will be enrolled.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or a legally acceptable representative(s), as required by local regulations, must give

written consent/assent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to subjects who have provided consent/assent (and assent as applicable) refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent/assent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

The total blood volume to be collected is considered to be within the normal range for blood collection from pediatric subjects.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the ICF, applicable recruiting materials,

and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent/assent

Each subject (parent/legal guardian and/or subject as per local regulations) must give written consent/assent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) and assent form that is/are used must be approved by both the sponsor and by the

reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent/assent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent/assent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent/assent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent/assent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent/assent, a copy of the ICF must be given to the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent/assent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent/assent of the subject or legally acceptable representative is obtained.

Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent/assent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. Written assent should be obtained from subjects who are able to write. A separate assent form written in language the subject can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the subject, and to the subject's parent and/or legally acceptable representative.

When prior consent/assent of the subject is not possible and the subject's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements.

The subject or legally acceptable representative must be informed about the study as soon as possible and give consent/assent to continue.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent/assent obtained from the subject (or his or her legally acceptable representative) includes explicit consent/assent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent/assent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory pharmacodynamic, biomarker, and PK research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and

IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent/assent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the CRF and will be considered source data:

- Race
- Blood pressure and pulse/heart rate
- Height and weight

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF (eCRF), and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Study site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the

investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last study assessment for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

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

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

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

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding DACOGEN or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent/assent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of DACOGEN, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all study sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that

the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Esther Rose, MD

Institution: Janssen Research & Development, LLC

Signature: [redacted] Date: 6-OCT-2015

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

LAST PAGE