CLINICAL STUDY PROTOCOL

Protocol Title:	Phase 1b/2 Study of Carfilzomib in Combination With Induction Chemotherapy in Children With Relapsed or Refractory Acute Lymphoblastic Leukemia
Protocol Number:	20140106 (formerly CFZ008)
Name of Investigational Product:	Carfilzomib for Injection
IND Number:	71,057
EudraCT Number:	2014-001633-84
NCT Number:	02303821
Sponsor:	Onyx Therapeutics, Inc., an Amgen Inc. subsidiary One Amgen Center Drive Thousand Oaks, California 91320 United States Phone: +1-805-447-1000 Fax: +1-805-480-4978
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Investigators:	**PHASE 1:** [redacted], MD Sorbonne Paris-Cité [redacted], MD Medical College of Wisconsin **PHASE 2:** [redacted], MD University of Colorado [redacted], MD Children's Hospital of Orange County [redacted], MD Erciyes University

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Date of Original Protocol:	11 April 2014
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Protocol Amendment 2	23 January 2015
Protocol Amendment 3	20 October 2016
Protocol Amendment 4	22 February 2017
Protocol Amendment 5	11 September 2017
Protocol Amendment 6	24 October 2018
Protocol Amendment 7	19 September 2019
Protocol Amendment 8	13 August 2020
Protocol Amendment 9	04 February 2021
Protocol Amendment 10	03 August 2021
Protocol Amendment 11	04 November 2022
Protocol Amendment 12	**28 August 2023**
Confidentiality Statement:	This material is the property of Onyx Therapeutics, Inc., a wholly owned subsidiary of Onyx Pharmaceuticals, Inc., an Amgen Inc. subsidiary. The material is highly confidential and is to be used only in connection with matters authorized by a senior representative of Onyx Therapeutics, Inc., and no part of it is to be disclosed to a third party without the express prior written permission of Onyx Therapeutics, Inc.
Compliance Statement:	This study will be conducted in accordance with Protocol 20140106, the International Council for Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the applicable country and regional (local) regulatory requirements.

PROTOCOL ACCEPTANCE PAGE

Protocol Number/Date: Protocol 20140106, Amendment **12**/**28 August 2023** I have read this protocol for Study 20140106 entitled: Phase 1b/2 Study of Carfilzomib in Combination With Induction Chemotherapy in Children with Relapsed or Refractory Acute Lymphoblastic Leukemia. As investigator, I understand and agree to conduct this study as outlined herein.

_____

Investigator Name (print)

_____ _____

Investigator Signature Date

Signature on this page assures the sponsor that, to the best of the investigator's knowledge, the affiliated Institutional Review Board (IRB)/Independent Ethics Committee (IEC) operates in accordance with the governing regulations, and that the investigator understands, and agrees to abide by, all governing regulatory obligations and the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and country and regional (local) requirements while conducting this clinical investigation. Once signed, the original of this form should be detached from the protocol and returned to the Sponsor or its designee (please retain a copy for your files).

1. Synopsis

<table>
<tr><td>Name of sponsor/company:</td><td>Onyx Therapeutics, Inc., an Amgen Inc. subsidiary</td></tr>
<tr><td>Name of product:</td><td>Carfilzomib for Injection</td></tr>
<tr><td>Title of study and protocol number and phase:</td><td>Phase 1b/2 Study of Carfilzomib in Combination with Induction Chemotherapy in Children with Relapsed or Refractory Acute Lymphoblastic Leukemia; 20140106 (formerly CFZ008).</td></tr>
<tr><td>Study objectives:</td><td>The phase 1 part of the study is now closed. Phase 2 starts from Section 17.11 Appendix K.
<u>Phase 2:</u>
All primary and secondary objectives will be analyzed for T-cell and B-cell acute lymphoblastic leukemia (ALL) populations separately, unless otherwise specified. For the primary and secondary endpoint evaluation, response will be derived by the sponsor based upon local reporting of bone marrow, peripheral blood, and extramedullary disease status. Minimal residual disease (MRD) status will be determined per central lab review of bone marrow MRD using next generation sequencing (NGS).
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>• Compare the rate of CR of CFZ-VXLD at the end of induction therapy to an appropriate external control.</td><td>• CR after induction therapy</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>• Evaluate the safety and tolerability of CFZ-VXLD</td><td>• Treatment-emergent and treatment-related adverse events and severe adverse events and laboratory abnormalities during the induction therapy and consolidation therapy</td></tr>
<tr><td>• Compare the rate of CR, CRp, CRh, and CRi of CFZ-VXLD at the end of induction therapy relative to an appropriate external control</td><td>• CR, CRp, CRh, and CRi at the end of induction therapy</td></tr>
<tr><td>• Compare EFS for CFZ-VXLD to an appropriate external control</td><td>• EFS, defined as time from initiation of therapy until treatment failure (defined as failure to reach at least a CRi after consolidation or after induction in subjects that do not receive consolidation), relapse, or death from any cause</td></tr>
<tr><td>• Compare OS for CFZ-VXLD relative to an appropriate external control</td><td>• OS defined as time from initiation of therapy until death from any cause</td></tr>
</table></td></tr>
</table>

	• Estimate the DOR for CFZ-VXLD relative to an appropriate external control	• DOR, defined as time from earliest of CR, CRp, CRh, or CRi to relapse or death from any cause
	• Estimate the rate of MRD[-] at the end of induction in subjects receiving CFZ-VXLD	• MRD status using NGS less than 10^{-4} after induction therapy in subjects achieving CR
	• Estimate the rate of MRD[-] bone marrow after induction and consolidation therapy in subjects with B-cell ALL **or T-cell ALL** receiving CFZ-VXLD	• MRD status using NGS less than 10^{-3} and less than 10^{-4} in subjects achieving CR, CRp, CRh, or CRi after induction and consolidation therapy**, separately**
	• Estimate the proportion of subjects that bridge to stem cell transplant or CAR-T cell therapy in subjects receiving CFZ-VXLD	• Occurrence of a stem cell transplant or CAR-T, without an intervening relapse after protocol specified therapy
	• Estimate the rate of CR, CRp, CRh, and CRi of CFZ-VXLD at the end of consolidation therapy in subjects receiving CFZ-VXLD	• CR, CRp, CRh, and CRi after consolidation therapy
	• Estimate the pharmacokinetics of carfilzomib when administered as part of VXLD regimen	• Carfilzomib pharmacokinetic parameters, including AUC, C_{max}, and if feasible, $t_{1/2}$
	AUC = area under the concentration-time curve; CAR-T = chimeric antigen receptor T cell therapy; CFZ-VXLD = carfilzomib combined with VXLD; C_{max} = maximum plasma concentration; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; CRp = complete remission with incomplete recovery of platelets; DOR = duration of response; EFS = event-free survival; MRD = minimal residual disease; MRD[-] = minimal residual disease negative bone marrow; NGS = next generation sequencing; OS = overall survival; $t_{1/2}$ = half-life; VXLD = vincristine, dexamethasone, PEG asparaginase, daunorubicin	
Study design:	This study is a phase 1b/2 study evaluating carfilzomib administered with a chemotherapy backbone. After the maximum tolerated dose (MTD) or recommended phase 2 dose is identified in the phase 1 part of the study, dosing in the phase 2 part of the study will begin. The phase 1 part of the study is now closed. **Phase 2:** The phase 2 portion of the study is a multicenter, single-group, externally-controlled study of carfilzomib in combination with vincristine, dexamethasone, polyethylene glycol (PEG)-asparaginase, daunorubicin (VXLD) in a minimum of 100 subjects, unless futility is met. Eligible subjects must be greater than or equal to 1 month to less than 21 years old, with their original diagnosis at less than 18 years of age, and must have ALL with bone marrow relapse (greater than or equal to 5% leukemia blasts in bone	

marrow) or refractory relapse with or without extramedullary disease of the T-cell phenotype or of the B-cell phenotype after having received a targeted B-cell immune therapy (eg, blinatumomab, inotuzumab, or chimeric antigen receptor T cell [CAR-T] therapy).

The carfilzomib dose for phase 2 will be 20 mg/m^2 on day 1 of induction and 56 mg/m^2 for subsequent doses.

Eligible subjects will be treated with VXLD plus carfilzomib for 1 cycle (induction), followed by assessment of treatment response. All subjects who do not show progression during induction will undergo a bone marrow and extramedullary disease evaluation after completion of induction therapy between days 29 to 45 of induction (subjects greater than or equal to 12 months of age) or days 36 to 50 of induction (subjects less than 12 months of age), based on blood count recovery but before the start of post-induction therapy, whichever comes first. Response will be assessed per local and central laboratory review of bone marrow, peripheral blood and differential, and local assessment for sites of extramedullary disease. MRD will be assessed by NGS central laboratory review and local evaluation by flow cytometry and/or PCR or NGS when available.

Subjects without disease progression after induction may, at the investigator's discretion, be treated with 1 cycle of consolidation chemotherapy plus carfilzomib. Subjects who do not show disease progression during consolidation will be assessed for treatment response between day 29 to 45 of consolidation (subjects greater than or equal to 12 months of age) or days 36 to 50 of consolidation (subjects less than 12 months of age), based on blood count recovery or start of alternative therapy, whichever comes first.

Treatment response after consolidation therapy will also be assessed per local and central laboratory review of bone marrow, peripheral blood and differential, and local assessment for sites of extramedullary disease.

Infants (less than 12 months at screening) will receive a modified induction and consolidation based on the Interfant-06 induction/consolidation. The modified induction/consolidation cycles for infants are 35 days in duration and response assessment will occur between 36 to 50 days.

When available local laboratory assessments of MRD by flow cytometry and/or PCR or NGS will be collected. The consolidation treatment will consist of one 28-day cycle of Children's Oncology group-modified Berlin-Frankfurt-Munster (BFM) therapy; cyclophosphamide, cytarabine, 6-mercaptopurine, PEG-asparaginase, vincristine, and intrathecal (IT) therapy or for less than 12 months of age a modified infant consolidation from COG AALL15P1; cyclophosphamide, cytarabine, 6-mercaptopurine, and IT therapy, combined with carfilzomib at a dose of 56 mg/m^2 (or lower if dose reduction was required during induction) at the same schedule as the induction therapy.

After completion of study therapy, subjects will be followed for subsequent treatment(s), event-free and overall survival.

For selected objectives, the treatment response to induction of subjects receiving CFZ-VXLD will be compared to an external control arm of subjects from an observational study of relapsed pediatric ALL (Study 20180065) that received standard-of-care (SoC)

	chemotherapy, after appropriate adjustment. More details will be included in the statistical analysis plan.
Number of investigational sites:	The phase 1 part of the study is now closed. **Phase 2:** Approximately 120 sites
Planned number of subjects:	The phase 1 part of the study is now closed. **Phase 2:** A minimum of 100 subjects will be enrolled and receive at least one dose of carfilzomib in the phase 2 part of the study unless futility is met. A minimum of 30 subjects with T-cell ALL and 50 subjects with B-cell ALL will be enrolled.
Sample size justification:	The phase 1 part of the study is now closed. **Phase 2:** The sample size was determined based on practical considerations and limited phase 1 data. Due to the rarity of the patient population, a minimum of 50 B-cell and 30 T-cell ALL subjects are planned to be enrolled, in order to reach more than 70% power for testing the primary hypothesis for at least one phenotype at 2-sided alpha of 0.05, with an interim futility analysis. The external control arm is expected to include **approximately 74** B-cell ALL subjects and **approximately 6**0 T-cell ALL subjects as per the **primary** analysis sets **(B-PAS/T-PAS)** included in Study 20180065. More details will be presented in the Study 20180065 protocol which will provide the data for the external control arm. Additionally, after appropriate propensity score adjustment, the complete remission (CR) rate is expected to be 25% for B-cell and 15% for T-cell **subjects** from the external control arm, and approximately 60% for B-cell and 30% for T-cell **subjects** from CFZ-VXLD arm. As these estimates are based on data **available so far**, additional scenarios proposed for the experimental arm **CR rates and sample sizes** and the power**/external control sample sizes** expected in these cases are included in Table 27.
Study population:	The phase 1 part of the study is now closed. **Phase 2:** All subjects must be greater than or equal to 1 month to less than 21 years of age and diagnosed **prior to their 18th birthday** with relapsed or refractory relapsed ALL. See Sections 21.1 and 21.2 for additional details.
Inclusion criteria:	The phase 1 part of the study is now closed. **Phase 2:** 110 Subject's legally acceptable representative has provided informed consent when the subject is legally too young to provide informed consent and the subject has provided written assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated, except for standard of care local testing as permitted per Section 21.3. 111 Age greater than or equal to 1 month to less than 21 years. Subjects greater than or equal to 18 years must have had their original diagnosis at less than 18 years of age. 112 Subjects must be diagnosed with relapsed or refractory relapsed ALL.

	113	Subjects must have a documented first remission, less than 5% blasts in the bone marrow (M1 bone marrow) and no evidence of extramedullary disease.
	114	T-cell ALL with bone marrow relapse (defined as greater than or equal to 5% leukemia blasts in bone marrow) or refractory relapse with or without extramedullary disease. OR B-cell ALL with bone marrow relapse or refractory relapse (defined as greater than or equal to 5% leukemia blasts in bone marrow) after having received a targeted B-cell immune therapy (eg, blinatumomab, inotuzumab, or a CAR-T therapy) with or without extramedullary disease.
	115	Adequate liver function: bilirubin less than or equal to 1.5 x upper limit of normal (ULN), alanine aminotransferase (ALT) less than or equal to 5 x ULN.
	116	Adequate renal function: serum creatinine less than or equal to 1.5 x ULN or glomerular filtration rate (GFR) greater than or equal to 70 mL/min/1.73 m^2; or for children less than 2 years of age, greater than or equal to 50 mL/min/1.73 m^2.
	117	Adequate cardiac function: shortening fraction greater than or equal to 30% or ejection fraction greater than or equal to 50%
	118	Karnofsky (subjects greater than or equal to 16 years of age) or Lansky (subjects 12 months to less than 16 years of age) performance status greater than or equal to 50%.
	119	Subjects must have fully recovered from the acute toxic effects of all previous chemotherapy, immunotherapy, or radiotherapy treatment before enrollment (for example: recovery from gastrointestinal toxicity may occur more rapidly than less reversible organ toxicities such as sinusoidal obstruction syndrome or non-infectious pneumonitis, for serious prior toxicities recommend discussion with Amgen medical monitor)
	120	Life expectancy of greater than 6 weeks per investigator`s judgment at time of screening
Exclusion criteria:	The phase 1 part of the study is now closed. **Phase 2:**	
	211	Prior treatment with carfilzomib.
	214	Intolerance, hypersensitivity, or inability to receive any of the chemotherapy components of the VXLD regimen (or acceptable substitutes as listed in Section 22.2.1.2). An exception is allowed for allergy to asparaginase products if Erwinia asparaginase is unable to be administered.
	215	Autologous hematopoietic stem cell transplantation (HSCT) within 6 weeks prior to start of study treatment.
	216	Allogeneic HSCT within 3 months prior to start of study treatment.
	217	Active graft versus host disease (GVHD) requiring systemic immune suppression.

218	Less than 30 days from discontinuation of immune suppressive therapy administered for the treatment of acute or chronic GVHD.
219	Isolated extramedullary relapse.
220	Positive bacterial or fungal infection within 14 days of enrollment (except for documented line infection, line has been removed, and blood culture after line removal is negative for 5 days prior to first dose of induction therapy). Antibiotics may be administered for prophylaxis as per institutional standards up to and after enrollment.
221	Subjects with less than 3 antibody half-lives since the last dose of monoclonal antibody (eg, 66 days for rituximab, 69 days for epratuzumab, inotuzumab for 36 days), prior to first dose of investigational product must be discussed with the Amgen medical monitor and may be allowed to enroll based on extent of disease or evidence of rapidly rising peripheral or bone marrow blast counts.
222	Cell-based immunotherapy (eg, donor leucocyte infusion, CAR-T cells, tumor vaccines) within 42 days prior to first dose of investigational product. If the Amgen medical monitor agrees, an exception may be granted to the 42-day requirement for subjects with rapidly rising peripheral or bone marrow blast counts.
223	Down's syndrome.
224	Presence of another active cancer.
225	History of grade greater than or equal to 2 pancreatitis within 6 months to screening
226	Unresolved toxicities from prior anticancer therapy, defined as not having resolved to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grade 1 or to levels dictated in the eligibility criteria apart from alopecia or toxicities from prior anticancer therapy that are considered irreversible and do not trigger another exclusion criterion (defined as having been present and stable for greater than 4 weeks)
227	Antitumor therapy (chemotherapy, investigational agents, molecular-targeted therapy) within 7 days of day 1 of induction. Exception: hydroxyurea to control peripheral blood leukemic cell counts is allowed until start of investigational product.
228	Active viral infection, including but not limited to cytomegalovirus (CMV), Hepatitis B infection with positive serum hepatitis surface antigen or hepatitis B DNA, human immunodeficiency virus (HIV), Hepatitis C with detectable hepatitis C RNA. Subjects who have previously received a stem cell transplant must be screened for CMV infection, unless both subject and donor are known to be CMV negative.
229	Currently receiving treatment in another investigational device or product study, or less than 14 days since ending treatment on another investigational device or product study.
230	Uncontrolled arrhythmias or screening ECG with corrected QT interval (QTc) of greater than 470 msec.

	231 History or evidence of any other clinically significant disorder, condition, or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion. 238 Known allergy to captisol (a cyclodextrin derivative used to solubilize carfilzomib; for a complete listing of Captisol-enabled drugs, see the Ligand Pharmaceuticals, Inc. website).
Treatment regimen(s)	The phase 1 part of the study is now closed. **Phase 2:** Carfilzomib will be administered at a dose of 20 mg/m^2 on day 1 followed by 56 mg/m^2 on days 2, 8, 9, 15, and 16 during induction and at 56 mg/m^2 on days 1, 2, 8, 9, 15, and 16 during the optional consolidation. **Induction VXLD:** For subjects greater than or equal to 12 months of age at screening: • Vincristine: 1.5 mg/m^2 per dose on days 1, 8, 15, and 22 (maximum single dose 2 mg) • Daunorubicin: 60 mg/m^2 per dose IV on day 2 • PEG-asparaginase (Erwinia Asparaginase for asparaginase allergic subjects): 2500 U/m^2 per dose IV on days 4 and 18, • Dexamethasone: 3 mg/m^2 per dose twice daily on days 1 through 21, total daily dose should be 6 mg/m^2 per day In regions unable to source components of VXLD, alternate forms at equivalent dose may be used. In addition, anthracycline may be omitted from the regimen, at the investigator's discretion, for subjects enrolling less than 6 months from stem cell transplant or CAR-T therapy or subjects in third or higher relapse, or in refractory relapse if the subjects most recent salvage therapy included an anthracycline. See Section 22.1.2.1 for details. See Table 17 for details regarding VXLD dosing for subjects less than 12 months of age at screening. **Modified BFM Consolidation:** For subjects greater than or equal to 12 months of age at screening: • Cytarabine: 75 mg/m^2 per dose IV or SC on days 1 through 4 and 8 through 11 • 6-mercaptopurine: 60 mg/m^2 per day orally on days 1 through 14 • Cyclophosphamide: 1 g/m^2 on day 1 • Vincristine: 1.5 mg/m^2 per dose on days 15 and 22 (maximum single dose 2 mg) • PEG-asparaginase (Erwinia Asparaginase for asparaginase allergic subjects or alternative agents; see Section 22.1.2.1): 1000 U/m^2 IV on day 15 See Table 21 for details regarding modified BFM consolidation dosing for subjects less than 12 months of age at screening. Intrathecal chemotherapy: For subjects greater than or equal to 12 months of age at screening:

	• CNS negative (at screening): methotrexate on days 1 and 8 • CNS positive (at screening): methotrexate, cytarabine, and hydrocortisone on days 1, 8, 15, and 22. • IT therapy on day 1 of induction may include cytarabine, methotrexate, or triple-therapy per institutional practice • Administration of IT therapy on day 29 is per institutional practice See Table 17 and Table 21 and for details regarding modified IT chemotherapy dosing for subjects less than 12 months of age at screening.
Criteria for evaluation:	The phase 1 part of the study is now closed. **Phase 2:** Response will be assessed per local and central laboratory review of bone marrow, peripheral blood and differential, and local assessment for sites of extramedullary disease.
Statistical methods and analyses:	The phase 1 part of the study is now closed. **Phase 2:** **Primary Analysis** The primary analysis for each phenotype will occur when the external control subjects **from B-PAS/T-PAS** have been selected and at least 100 enrolled subjects in the experimental arm have received at least one dose of carfilzomib and had the opportunity to complete a post-induction response evaluation. All the available data on primary/secondary and exploratory endpoints will be summarized at this time. **Final Analysis** The final analysis will occur after the end of the study for all **subjects**. For each planned analysis, data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan with the expectation that all outstanding data issues are resolved ahead of the snapshot. The data will be locked to prevent further changes, and a snapshot of the locked database will be used in the analysis. **Efficacy Analyses** Unless otherwise specified all efficacy endpoints will be analyzed for B-cell and T-cell phenotype independently. The comparison analyses for CR, CRh, CRp, CRi, EFS, and OS endpoints will use the Primary Analysis Set, while for all the other efficacy endpoints the Safety Analysis Set will be used. **Interim Futility Analysis** An interim analysis for futility will be conducted independently for each phenotype **T-cell and B-cell, respectively**. The analysis will occur after **at least 60** subjects **from the experimental arm** have received at least one dose of carfilzomib and had the opportunity to complete a post induction response evaluation. The futility criterion will be derived such that the probability of futility is **at least 70% under H0 and the power loss is at most** 0.0**1** under H1**,** using a Bayesian predictive probability approach. Additional details are provided in the SAP.

	Safety Analyses The safety analyses will be based on the Safety Analysis Set analyzed by each phenotype separately.
Correlative studies:	The phase 1 part of the study is now closed. **Phase 2:** For pharmacokinetic analyses [redacted] assessments refer to Sections 24.2.6 and 24.2.7. Samples for genomic biomarker analysis will not be collected in phase 2.

TABLE OF CONTENTS

Phase 2 of study begins at Section 17.11.1 through Section 30 (Appendix K)

[redacted]

List of Tables

List of Figures

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADL	activities of daily living
AE	adverse event
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	aspartate aminotransferase
AUC	area under the curve
BFM	Berlin-Frankfurt-Münster
BID	bis in diem (twice a day)
BLR	Bayesian Logistic Regression
B-PAS	**B-cell primary analysis set**
BSA	body surface area
BUN	blood urea nitrogen
Captisol	sulfobutylether beta cyclodextrin (SBE beta CD)
CAR-T	chimeric antigen receptor T cell therapy
CBC	complete blood count
C_{max}	maximum plasma concentration
CMP	carfilzomib, melphalan, prednisone
CMV	cytomegalovirus
CNS	central nervous system
COG	Children's Oncology Group
Cr	serum creatinine
CR	complete remission
CRF	case report form
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete hematologic recovery
CRp	complete remission without platelet recovery
CSF	cerebral spinal fluid
CSRC	Cohort Safety Review Committee

Abbreviation	Definition
CTCAE	Common Terminology Criteria for Adverse Events
CT-L	chymotrypsin-like
CYP450	cytochrome P450
D5W	5% Dextrose Injection, USP
DFS	disease-free survival
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	End of Treatment
EU	European Union
FDA	Food and Drug Administration
FCBP	females of childbearing potential
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulation factor
GFR	glomerular filtration rate
GGT	gamma-glutamyltransferase
GVHD	graft versus host disease
H2	histamine 2 blocker
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplantation
HSV	herpes simplex virus
IB	investigator's brochure
IBG	Independent Biostatistics Group
ICF	informed consent form
ICH	International Council on Harmonisation
ID	induction death
IEC	Independent Ethics Committee
Ig	immunoglobulin
IM	intramuscular
IMiD	immunomodulatory drug

Abbreviation	Definition
IND	Investigational New Drug
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IST	investigator-sponsored trial
IT	intrathecal
IUD	intrauterine device
IV	intravenous(ly)
IVIg	intravenous immunoglobulin
IVRS	Interactive Voice Recognition System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MTD	maximum tolerated dose
M-W-F	Monday, Wednesday, Friday
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCRM	new continual reassessment method
NE	not evaluable
NGS	next generation sequencing
NM-GRF	nuclear magnetic-glomerular filtration rate
ORR	overall response rate
PAS	**primary analysis set**
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
[redacted]	[redacted]
PEG	polyethylene glycol
P-gp	P-glycoprotein
PK	pharmacokinetics
PN	peripheral neuropathy
PR	partial response
PRES	posterior reversible encephalopathy syndrome
QTc	corrected QT interval
R3 backbone	dexamethasone, mitoxantrone, PEG-asparaginase, and vincristine
RBC	red blood cell
[redacted]	[redacted]

Abbreviation	Definition
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SD	stable disease
SIADH	syndrome of inappropriate secretion of antidiuretic hormone
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TACL	Therapeutic Advances in Childhood Leukemia & Lymphoma
TcR	T-cell receptor
TLS	Tumor Lysis Syndrome
T_{max}	time to maximum plasma concentration
TMP-SMX	trimethoprim-sulphamethoxazole
T-PAS	**T-cell primary analysis set**
TPMT	thiopurine methyltransferase
UK	United Kingdom
ULN	upper limit of normal
US	United States
VXLD	In Section 3 BACKGROUND INFORMATION: vincristine; dexamethasone; PEG-asparaginase; doxorubicin or daunorubicin In all other sections: vincristine, dexamethasone, PEG-asparaginase, daunorubicin
WBC	white blood cell
[redacted]	[redacted]
[redacted]	[redacted]

PHASE 1 PORTION OF STUDY

3. Background Information

Phase 1 is now closed, the phase 2 protocol, including the phase 2 background information is provided in Appendix K.

3.1 Disease Background

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood. Approximately 2400 children in the United States (US) are newly diagnosed with this disease each year. The peak incidence occurs among 2 to 3-year-olds, with a rate of 80 cases per million for this age group. There is no disparity in incidence by sex, but white children are affected up to three-fold as often as black children (SEER Research Data 2013).

The epidemiology of pediatric ALL does not vary much among western nations, with the reported incidence typically approximating 3 to 4 cases per 100,000 children (NCIC 2004; Milne 2008; Hjalgrim 2003; Dalmasso 2005). In some reports, the ALL incidence among boys slightly exceeds that in girls (Kulkarni 2011; Milne 2008). The overall incidence of ALL appears to be stable over time (NCIC 2004; Kulkarni 2011; Milne 2008; Hjalgrim 2003), however Dalmasso et al. have described a recent increase in pediatric ALL cases in Italy (Dalmasso 2005).

Although the majority of children with newly diagnosed ALL will achieve a complete remission and enjoy long-term survival, approximately 20% will experience bone marrow relapse. A 2010 report by Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL) presented the remission rates and disease-free survival (DFS) of children with relapsed lymphoblastic leukemia treated between 1995 and 2004 at institutions participating in their consortium. While children with either an early or late first bone marrow relapse fared well (83% and 93% complete remission, respectively), children with subsequent relapses had a progressively lower likelihood of achieving remission again. Only 44% of children with a second bone marrow relapse achieved complete remission and their 5-year DFS was 27%. Those with a third relapse achieved a subsequent complete remission only 27% of the time and their 5-year DFS was a mere 15%. These figures clearly demonstrate the need for novel agents to improve outcomes for very high-risk patients.

Salvage therapy for subjects with relapsed ALL most often involves combinations of agents with activity in newly diagnosed ALL, used at varying dose levels and schedules. Key agents in this setting include: etoposide, vincristine, asparaginase, doxorubicin, mitoxantrone, cytarabine, cyclophosphamide, methotrexate, dexamethasone, and prednisone. Current standard of care therapies for relapsed ALL include salvage regimens such as the UK R3 (R3; dexamethasone, mitoxantrone, PEG-asparaginase, and vincristine) and VXLD (vincristine; dexamethasone; PEG-asparaginase; and doxorubicin or daunorubicin) chemotherapy backbones. The addition of a proteasome inhibitor to these backbones could further boost clinical response through a mechanism of action that differs from any of the current chemotherapy agents in the R3 or VXLD regimens.

Novel agents for the treatment of pediatric ALL have been developed in recent years and, like proteasome inhibitors, offer promise for improved outcomes. Clofarabine (Clolar), a second-generation purine analogue that received accelerated approval in the

US in 2004, is indicated for the treatment of patients 1 to 21 years old with ALL who have had at least 2 treatment regimens and for whom ALL has recurred or resisted treatment. Clofarabine has considerably greater activity, both as a single agent and in combination, relative to first generation purine nucleoside analogue antecedents. Approval was based on improved response rate and no survival advantage has been demonstrated to date. Nelarabine (Arranon), a nucleoside metabolic inhibitor that received accelerated approval in the US in 2005, is indicated for the postinduction treatment of patients with T-cell ALL and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens. Nelarabine has demonstrated activity as monotherapy in T-cell ALL in the pediatric and adult populations. Neither Clofarabine nor Nelarabine is currently approved for use in combination with induction chemotherapy. Blinatumomab (Blincyto®), developed by Amgen, Inc., is an antibody with specificity for both CD19 and CD3, and attacks B-cell lymphoblastic leukemia using bispecific T-cell-engaging technology. Blinatumomab has received approval in the United States for the treatment of adults and children with Philadelphia chromosome-negative relapsed or refractory and minimal residual disease (MRD)-positive B-cell precursor ALL. In the European Union (EU), approval for this indication is currently limited to adults only. Ongoing research is needed to determine the best approach for incorporating these agents into the treatment armamentarium for relapsed and/or high-risk pediatric ALL.

Minimal residual disease has well-established prognostic utility in pediatric ALL (Cavé 1998). A matched case-control study by Sutton et al. found that bone marrow MRD measure by real-time polymerase chain reaction (PCR) on Day 15 of induction was strongly predictive of relapse (Sutton 2009). MRD has also demonstrated prognostic utility prior to hematopoietic stem cell transplantation (HSCT), with poorer survival among those who enter HSCT with MRD positivity (Campana 2013). The effect of proteasome inhibition on MRD has yet to be determined but is being explored using flow cytometric analysis in the Phase 2 part of a study of bortezomib in pediatric ALL. Most children with multiply relapsed ALL or relapsed ALL with other high-risk features will proceed to allogeneic HSCT, thus reduced MRD due to proteasome inhibition could significantly impact prognosis beyond the effect of improving complete remission rates alone. The study presented in this protocol will be the first, to our knowledge, to explore MRD following proteasome inhibition using a quantitative PCR technique.

3.2 Proteasome Inhibitors

The proteasome is a multicatalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within normal and transformed cells. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are cleaved within the proteasome by 1 or more of 3 separate N-terminal threonine protease activities: a chymotrypsin-like (CT-L) activity, a trypsin-like activity, and/or a caspase-like activity.

Treatment with proteasome inhibitors produces an accumulation of pro-apoptotic proteins, promotes autophagy, and increases the stability of negative cell cycle regulators (Shen 2013; Zang 2012). Data from pediatric-derived cell lines presented at the American Society of Hematology (ASH) meeting in December 2013, indicated substantial cytotoxic activity in all leukemia cells treated with carfilzomib (Jayanthan 2013). This is consistent with the work of Niewerth et al. who reported the susceptibility of numerous patient-derived pediatric leukemia specimens to bortezomib, carfilzomib, and other investigational proteasome inhibitors. A strong correlation with the relative proportion of immunoproteasomes to constitutive proteasomes was suggested and may explain the greater sensitivity to proteasome inhibition of lymphoblastic as compared with myeloid leukemias (Niewerth 2013). Clinical data comes from the proteasome inhibitor bortezomib which shows the same maximum tolerated dose (MTD) as in adults, when assessed in pediatric subjects with solid tumors or acute leukemias (1.2 and 1.3 mg/m^2, respectively) (Blaney 2004; Horton 2007). While no evidence of activity was seen in subjects with solid tumors, a suggestion of a positive signal occurred in subjects with leukemia. A subsequent Phase 1 study by Messinger, et al. using bortezomib 1.3 mg/m^2 added to the chemotherapy combination of vincristine, dexamethasone, PEG-asparaginase, and doxorubicin (VXLD) showed activity with acceptable toxicity in children with relapsed ALL (Messinger 2010). A follow-up pediatric Phase 2 part of the study of bortezomib-VXLD in patients with relapsed B-cell ALL reported 70% complete remission, a remission rate that greatly exceeded the approximate 40% in comparable subjects from earlier studies (Messinger 2012).

3.2.1 Preclinical Background for Investigational Drug

Carfilzomib (formerly known as PR-171) is a tetrapeptide epoxyketone-based inhibitor of the chymotrypsin-like activity of the 20S proteasome. Carfilzomib, which is structurally and mechanistically different from the dipeptide boronic acid proteasome inhibitor bortezomib, showed less off-target activity when measured against a broad panel of

proteases including metallo-, aspartyl-, and serine proteases compared to bortezomib; the latter showed off-target inhibitory activity in the nanomolar range against several serine proteases (Arastu-Kapur 2009). This selectivity may be responsible for the reductions in myelosuppression and neuropathy observed in preclinical studies comparing carfilzomib with bortezomib.

Based on in vitro and in vivo studies, it is anticipated that a more intense and sustained proteasome inhibition can be achieved with carfilzomib relative to bortezomib, resulting in enhanced antitumor activity. Continuous 72-hour exposure to carfilzomib was associated with potent cytotoxic and pro-apoptotic activity across a broad panel of tumor-derived cell lines in culture (Demo 2007). Incubation of hematologic tumor cell lines with carfilzomib for as little as 1 hour led to rapid inhibition of proteasome activity followed by accumulation of polyubiquitinated proteins and induction of apoptotic cell death. Carfilzomib was also cytotoxic in bortezomib-resistant tumor cell lines (Suzuki 2011; Kuhn 2007).

Preclinical studies in rats and monkeys have been performed administering carfilzomib intravenously (IV) for 5 consecutive days followed by 9 days of rest for 2 cycles. Proteasome inhibition of more than 80% was achieved, suggesting that high-level inhibition of the proteasome with the epoxyketone class is possible, affording new opportunities to escalate dose to optimize antitumor effects (Onyx data on file, and Yang 2011). This finding was in contrast to preclinical testing with the boronate class of inhibitors that prohibited uninterrupted daily dosing due to substantial morbidity and mortality. Carfilzomib has also been administered to rats and monkeys for 6 and 9 months, respectively (once daily x 2: once daily dosing for 2 consecutive days for 3 weeks on a 28-day cycle). Carfilzomib was well tolerated at doses resulting in more than 80% proteasome inhibition, with no behavioral or histological evidence of peripheral neuropathy (PN) and no neutropenia (Onyx data on file and Carfilzomib Investigator's Brochure [IB]). In contrast, rats and monkeys treated with bortezomib in chronic toxicity studies were shown to have reduced motor activity, convulsions, tremors, and hind-limb paralysis accompanied by histological degeneration in peripheral nerves, as well as significant neutropenia (Velcade [bortezomib] full prescribing information [Millennium Pharmaceuticals 2012] and Velcade Summary of Product Characteristics [SmPC] [High Wycombe, Bucks, UK 2012]).

3.2.2 Clinical Background for Investigational Drug

As of 10 July 2015, approximately 2921 individual subjects have been treated with carfilzomib as participants in Onyx-sponsored clinical studies, and 89 subjects have been enrolled in studies in Japan sponsored by Ono Pharmaceutical Company. Approximately 3549 subjects have been treated with carfilzomib through the 76 completed or actively enrolling investigator-sponsored trials (ISTs) (Carfilzomib IB).

There are five Phase 3 studies in multiple myeloma: PX-171-009 (ASPIRE), PX-171-011 (FOCUS), 2011-003 (ENDEAVOR), 2012-005 (CLARION), and 20140355 (A.R.R.O.W.). Additionally, 137 subjects with solid tumors have been treated with carfilzomib.

These trials have explored various doses of carfilzomib either as monotherapy or in combination with other agents and in the majority of studies conducted to date, carfilzomib has been administered on 2 consecutive days for 3 weeks in a 28-day cycle. Carfilzomib clinical activity has been demonstrated in these studies along with an acceptable safety profile.

Higher doses of carfilzomib administered on a twice-weekly schedule have been studied. PX-171-007, a Phase 1b/2 study, was the first to establish the MTD of single agent carfilzomib administered as a 30-minute infusion in subjects with relapsed and/or refractory multiple myeloma (Papadopoulos 2015). Subjects received carfilzomib monotherapy on Days 1, 2, 8, 9, 15, and 16 of a 28-day cycle. Cycle 1 Day 1 and Day 2 doses were 20 mg/m^2 followed thereafter by dose escalation to 36, 45, 56, or 70 mg/m^2. Carfilzomib was administered later with low-dose dexamethasone (40 mg/week) at the 45 mg/m^2 and 56 mg/m^2 dose levels. Thirty-three subjects were treated and there were dose-limiting toxicities (DLTs) in 2 subjects dosed at 70 mg/m^2 of renal tubular necrosis (Grade 3) and proteinuria (Grade 3). The MTD was determined to be 56 mg/m^2.

In the 56 mg/m^2 cohort (n = 24), the most common treatment-related adverse events (AEs) of any grade were nausea (54.2%), dyspnea (50.0%), fatigue (45.8%), pyrexia (41.7%), and thrombocytopenia and chills (both 37.5%); a majority were Grade 1 or 2. At this dose, hematologic AEs of thrombocytopenia (37.5%) and anemia (16.7%) were the most common treatment-related AEs of ≥ Grade 3. When carfilzomib at 56 mg/m^2 was combined with dexamethasone (n = 8), nausea (25%), fatigue (25%), and dyspnea and chills (each 12.5%) occurred less frequently than with carfilzomib alone. The overall response rate (ORR) was 50% in the 56 mg/m^2 cohort where the majority of subjects

were refractory to IMiDs and bortezomib. The Phase 2 PX-171-003 – Part 2 (A1) study with single agent carfilzomib at 20/27 mg/m^2 in a similar population had an ORR of 22.9% in the Safety population.

Additional information on the safety and activity of carfilzomib is described in the Carfilzomib IB.

3.3 Dose Rationale

Carfilzomib has been evaluated as a single agent and as part of a combination regimen for the treatment of adult subjects with multiple myeloma. Carfilzomib has not been previously studied in children. The MTD for single-agent carfilzomib administered by IV infusion over 30 minutes on 2 consecutive days per week has been determined to be 56 mg/m^2 (Study PX-171-007). In combination with melphalan and prednisone, the MTD of carfilzomib administered on this same schedule has been determined to be 36 mg/m^2 (Kolb 2012). Assuming no substantial differences in metabolism of carfilzomib between adults and children, these clinical data in adults suggest that the MTD for carfilzomib combined with chemotherapy is likely to occur in the range of 36 to 56 mg/m^2 with twice weekly dosing. The current planned dose range of 27 to 70 mg/m^2 on twice weekly schedule spans either side of this range by 1 dose level.

Current practice is to start with 20 mg/m^2 of carfilzomib before escalating to a higher dose. The approved regimen for carfilzomib monotherapy includes escalation on Day 1 of Cycle 2. All other ongoing clinical trials of carfilzomib escalate on Day 8 of Cycle 1.

The first generation proteasome inhibitor, bortezomib, when used at the approved dose and schedule for multiple myeloma, has been shown to have clinical activity in pediatric subjects with ALL when used concurrently with a VXLD backbone (Messinger 2010).

Carfilzomib is primarily metabolized by epoxide hydrolase and peptidase, which are expected to be fully functional in pediatric populations (Auricchio 1981; McCarver 2002; Omiecinski 1994). Carfilzomib dosing will be adjusted based on body surface area (BSA) of the individual subject. Pharmacokinetic (PK) simulations for likely exposure achieved in pediatric populations based on an adult population PK model have been conducted. The simulation model supports a carfilzomib starting dose of 20 mg/m^2 for the initial pediatric study followed by a 27, 36, and 45 mg/m^2 dose-escalation scheme. Based on the available data in adults with multiple myeloma, we anticipated the MTD to be close to 36 mg/m^2/dose. However, the 45 mg/m^2 dose level was recently found to be tolerable and to date the 56 mg/m^2 dose level has yet to identify an MTD.

Preliminary pharmacokinetic data in children who received 20, 27, 36, 45, and 56 mg/m^2 of carfilzomib suggested that carfilzomib exposures were dose proportional across this range and did not differ significantly comparing ages 1 to 5, 6 to 12, and >12 years. Compared to adults, the geometric mean of dose normalized exposures (C_{max} and AUC) was similar, considering the high pharmacokinetic variability observed. Prior to protocol amendment 6, preliminary PK analyses on the first 3 dose levels up to 36 mg/m^2 had found an approximate 40% reduction in exposures in children versus adults and was used to support protocol amendment 6 to add the current 56 and 70 mg/m^2 dose levels. These findings suggest that the MTD is likely to be in the upper part of the 36 to 56 mg/m^2 dose range.

Prior to Protocol Amendment 3, 11 subjects (8 of them DLT evaluable) were treated with carfilzomib (20 or 27 mg/m^2) in combination with the R3 chemotherapy backbone (hereafter referred to as Dose Escalation 1); the MTD was determined to be 27 mg/m^2. This MTD was lower than anticipated, and some of the toxicity observed is hypothesized to have been caused by the R3 chemotherapy backbone. Dose Escalation 2 (combining carfilzomib with a VXLD [vincristine, dexamethasone, PEG-asparaginase, daunorubicin] chemotherapy backbone) was introduced to test this hypothesis. Because 20 mg/m^2 (Dose Level 1) is lower than the MTD of carfilzomib in combination with the likely more toxic R3 chemotherapy backbone, the dose escalation of carfilzomib in combination with the VXLD chemotherapy backbone will start at 27 mg/m^2 (Dose Level 2).

4. Study Objectives

The phase 2 protocol, including the phase 2 objectives is provided in Appendix K.

4.1 Primary Objectives

The primary objectives of this study are:

- To assess the safety and tolerability of carfilzomib, alone and in combination with induction chemotherapy, for the treatment of children with relapsed or refractory ALL
- To determine the MTD of carfilzomib in combination with induction chemotherapy and to recommend a phase 2 dose of carfilzomib in combination with induction chemotherapy

4.2 Secondary Objectives

The secondary objectives of this study are:

- To characterize the PK of carfilzomib alone and in combination with induction chemotherapy

- To evaluate the combined rate of bone marrow CR and bone marrow CRp at the end of the Induction Cycle
- To estimate the proportion of subjects who achieve MRD status $< 10^{-3}$ and $< 10^{-4}$ lymphoblasts at the end of the Induction Cycle

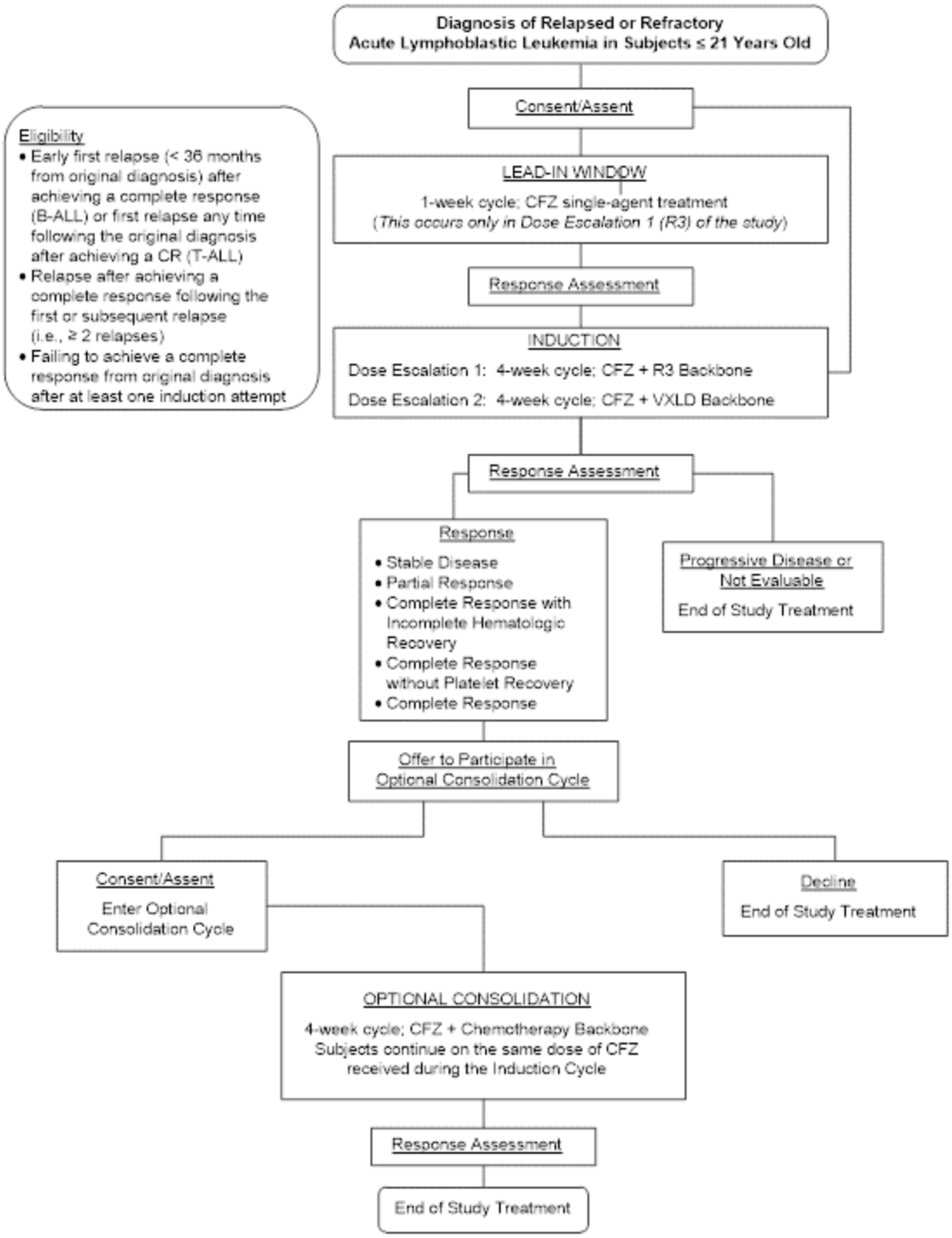
[redacted]

[redacted]

5. Study Design

The phase 2 protocol, including the phase 2 part of the study design is provided in Appendix K.

Figure 1. Phase 1b Schema



5.1 Type/Design of Study

This is a nonrandomized, multicenter, Phase 1b dose-escalation study of carfilzomib in combination with induction chemotherapy, comprising either an R3 backbone of dexamethasone, mitoxantrone, PEG-asparaginase, and vincristine (Dose Escalation 1)

or a VXLD backbone of vincristine, dexamethasone, PEG-asparaginase, and daunorubicin (Dose Escalation 2) in children with relapsed or refractory ALL.

Subjects who were 21 years old or younger at the time of their initial ALL diagnosis will be enrolled at approximately 50 pediatric oncology centers located in the US, Canada, Australia, Israel, or Europe. Approximately 18 subjects will participate in the R3 dose escalation and approximately 24 will participate in the second dose escalation for VXLD. Additional subjects may be enrolled to treat up to 12 subjects at the MTD.

Every effort will be made to enroll a minimum of 3 subjects who fall into each of the following age groups at the time of their enrollment onto this study:

- 12 to < 24 months old
- 2 to < 12 years old
- 12 to 18 years old
- A minimum number for subject enrollment will not be applied to subjects over 18 years of age. No infants (< 12 months of age) will be enrolled, although subjects originally diagnosed with ALL during infancy are eligible if they are at least 12 months old at the time of study treatment initiation.

There is no predetermined maximum number of subjects per age group, however, the sponsor may temporarily or permanently close enrollment to a particular age group, if the distribution of subjects across age groups appears imbalanced.

During the Dose Escalation 1 (R3) portion of the study only, the Induction Cycle will be preceded by a 1-week carfilzomib single-agent Lead-in Window. Subjects in both dose escalation portions of the study will receive a 4-week cycle of induction chemotherapy and have the option to receive a 4-week cycle of consolidation chemotherapy, if SD or better response is achieved at the end of the Induction Cycle. Refer to the Study Design Schema (Figure 1) and to Section 8, Dosage and Treatment Administration, for further details about the treatment regimen.

5.2 Dose-escalation Plan

The Phase 1b dose-escalation design will use the Bayesian 2-parameter logistic regression model, the new continual reassessment method (NCRM) applied to observed DLTs occurring during the Lead-in Window and Induction Cycle (Neuenschwander 2008). The prior distribution and the data available after each dose cohort are applied to an algorithm that computes the posterior distribution of the DLT rate at each dose level. The posterior probabilities of the estimated DLT rate at each dose to fall into target

toxicity interval (20%-33%) or excessive/unacceptable toxicity interval (> 33%–100%) will be used in the dose-escalation decision and the final determination of the MTD.

A cohort size of 2 will be used in Dose Escalation 1 (R3). The starting dose is 20 mg/m^2; the maximum planned dose and the minimum planned dose are 45 mg/m^2 and 20 mg/m^2, respectively. One or more cohorts of 2 subjects may be enrolled to each dose level, depending on the toxicity observed. The Cohort Safety Review Committee ([CSRC]; whose membership is described in Section 13.4) will review the safety data and dose level recommended by the algorithm after every cohort has completed the 4-week Induction Cycle. The CSRC will expand the dose level by 2 subjects, advance to the next dose level, or de-escalate to a lower dose level, based on the available data. No dose-level skipping will be allowed in dose-escalation decisions. There is no such constraint on de-escalation decisions. The algorithm will stop when the sample size reaches 18 or when the DLT rate of the recommended MTD has a 95% posterior credible interval that falls within the prespecified range of 5% to 60%.

A cohort size of 3 will be used in Dose Escalation 2 (VXLD). The starting dose level is 27 mg/m^2; the planned dose levels are 27, 36, 45, 56, and 70 mg/m^2. One or more cohorts of 3 subjects may be enrolled to each dose level, depending on the toxicity observed. The CSRC will review the safety data and dose level recommended by the algorithm after every cohort has completed the 4-week Induction Cycle. The CSRC will expand the dose level by 3 subjects, advance to the next dose level, or de-escalate to a lower dose level, on the basis of the available data. No dose-level skipping will be allowed in dose-escalation decisions. There is no such constraint on de-escalation decisions. If clinically justified, CSRC may halt enrollment and recommend the MTD or the dose for the phase 2 part of the study based on available data. More details are presented in the CSRC charter (see Section 13.4). The algorithm will stop when the sample size reaches 24 or if both of the first two criteria, or the third criterion are met:

- The probability of the Target Toxicity interval at the candidate MTD exceeds 40%

AND

- A minimum of 2 cohorts (6 subjects) are accrued and treated at the candidate MTD

OR

- The algorithm recommends a dose level that has been recommended twice and with 6 subjects treated, and the CSRC agrees with the recommendation

A minimum of 2 subjects (1 cohort) will be enrolled at the starting dose level in Dose Escalation 1 (R3). For the NCRM, the relationship between dose and the probability of DLT will be updated as additional subject safety information becomes available (eg, after the last subject in the cohort completes the Induction Cycle). After all subjects enrolled at the starting dose level are DLT-evaluable, the Bayesian Logistic Regression (BLR) model will be updated, and the NCRM will recommend the next dose level from the updated probabilities for target toxicity interval and excessive/unacceptable toxicity interval. The next dose level (eg, the Dose Level 2 or continuation of Dose Level 1) will be the dose with the highest posterior probability of having a toxicity rate in the target toxicity interval, which is defined as 20%–33%, and will be subject to the constraint that the probability of excessive/unacceptable toxicity, which is defined as > 33%-100%, is less than 40%. The MTD will be selected based on the above criteria or the stopping criteria as specified in Section 5.2 and the recommendation of the CSRC.

A minimum of 3 subjects (1 cohort) will be enrolled at the starting dose level in Dose Escalation 2 (VXLD).

When the algorithm recommends an MTD, the CSRC will review the data and recommend a dose for the Phase 2 part of the study.

5.3 Estimated Study Duration and Study Closure

The total study duration is expected to be a minimum of 48 months. Therefore, it is estimated that the final analysis will occur approximately 4 months after the last subject is enrolled. The study will be considered complete when the last subject has finished study treatment and all required follow-up assessments.

6. Subject Eligibility

The phase 2 protocol, including details on phase 2 subject eligibility are provided in Appendix K.

6.1 Inclusion Criteria

Inclusion criteria for the phase 1b part of the study are the following:

1. Age 21 years or younger at the time of initial ALL diagnosis and age > 1 year at the time of study treatment initiation.
2. Subjects must have a diagnosis of ALL with ≥ 5% blasts in the bone marrow (M2 or M3 disease), with or without extramedullary disease.
   - To be eligible, subjects must have had 1 or more prior therapeutic attempts, defined as:
     - Early first relapse (< 36 months from original diagnosis) after achieving a CR (B-ALL) or first relapse any time following the original diagnosis after achieving a CR (T-ALL)

       OR

     - First refractory bone marrow relapse occurring any time after original diagnosis after achieving a CR (ie, ≥ 1 failed attempt to induce a second remission)

       OR

   - Relapse after achieving a CR following the first or subsequent relapse (ie, ≥ 2 relapses)

     OR

   - Failing to achieve a CR from original diagnosis after at least 1 induction attempt
3. Subjects must have fully recovered from the acute toxic effects of all previous chemotherapy, immunotherapy, or radiotherapy treatment before enrollment.
4. Subjects must have a serum creatinine level that is ≤ 1.5 x institutional upper limit of normal (ULN) according to age. If serum creatinine level is > 1.5 x ULN, the subject must have a calculated creatinine clearance or radioisotope glomerular filtration rate (GFR) ≥ 70 mL/min/1.73 m^2, or for children < 2 years of age, ≥ 50 mL/min/1.73 m^2.
5. Adequate liver function, defined as both of the following:
   - Total bilirubin ≤ 1.5 x institutional ULN, except in the presence of Gilbert syndrome. For those with hyperbilirubinemia due to Gilbert syndrome, subjects are only eligible if they have a direct bilirubin ≤ 1.5 x institutional ULN.
   - Alanine aminotransferase (ALT) ≤ 5 x institutional ULN
6. Performance status: Karnofsky or Lansky scores ≥ 50 for subjects > 16 years old or ≤ 16 years old, respectively. See Appendix F
7. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test within 48 hours prior to study treatment initiation.
8. Females of childbearing potential and male subjects who are sexually active with a FCBP must agree to use a highly effective method of contraception plus a male condom during the study and for 6 months following the last dose of study

treatment. The methods of contraception are defined in the ICF. Where required by local laws, regulations and/or guidelines, additional country-specific requirements are outlined in a country-specific protocol supplement.

9. Subjects must provide written informed consent and pediatric assent in accordance with federal, local, and institutional laws and regulations.

6.2 Exclusion Criteria

Exclusion criteria for the phase 1b part of the study are the following:

1. Known allergy to any of the drugs used in the study.
   (Subjects who have had a previous allergy to PEG-asparaginase are eligible and if able, may receive Erwinia asparaginase at the investigator's discretion.)
2. Known allergy to Captisol (a cyclodextrin derivative used to solubilize carfilzomib; for a complete listing of Captisol-enabled drugs, see the Ligand Pharmaceuticals, Inc. website)
3. Left ventricular fractional shortening $< 30\%$
4. History of $\geq$ Grade 2 pancreatitis
5. Active graft-versus-host disease requiring systemic treatment
6. Positive culture for or other clinical evidence of infection with bacteria or fungus within 14 days of the initiation of study treatment
7. Down Syndrome
8. Prior therapy restrictions:
   - Subjects must have completed therapy with granulocyte-colony stimulating factor (G-CSF) or other myeloid growth factors at least 7 days before study treatment initiation, or at least 14 days before study treatment initiation, if pegylated myeloid growth factors were administered.
   - Subjects must have received the last dose of a non-monoclonal antibody biologic agent at least 7 days before study treatment initiation. For agents that have known adverse events (AEs) occurring beyond 7 days after the last administration, this period must be extended beyond the time during which AEs are known to occur, and the Sponsor study medical monitor should be contacted.
   - At least 3 antibody half-lives must have elapsed since the last dose of monoclonal antibody (eg, 66 days for rituximab, 69 days for epratuzumab, and 36 days for inotuzumab) before subjects may initiate study treatment.
   - Subjects must have completed any type of active immunotherapy (eg, tumor vaccines) at least 42 days before study treatment initiation.
   - Subjects must not have received other antineoplastic agents with therapeutic intent, excluding hydroxyurea and antimetabolites administered as part of maintenance chemotherapy, within 7 days prior to study treatment initiation.
9. Females who are pregnant and/or breastfeeding
10. Hepatitis B infection with positive hepatitis B DNA

7. Subject Screening and Enrollment

The phase 2 protocol, including details on phase 2 screening and enrollment are provided in Appendix K.

An informed consent form (ICF) must be signed and dated by the subject or the subject's legally acceptable representative before any study-specified tests may be performed. A signed and dated pediatric assent form must also be obtained, in accordance with local laws and regulations, prior to performing any study-specified tests on a child of appropriate age and development. Subjects who reach the age of majority during study participation must sign a new ICF, in order for study participation to continue.

Subjects are assigned an identification number when informed consent has been obtained. The subject identification number will be assigned by Interactive Web Response System (IWRS). This number is used to identify the subject throughout the study and must appear on all study-related documentation and communications.

Eligibility and enrollment of subjects will ultimately be determined by the investigator; however, in the phase 1b part of the study, the study medical monitor will first review results of the required screening assessments and may provide feedback to the investigator. Screening assessments are presented in Table 1 and, where needed, are further described in the text that follows. Evaluations performed as part of routine medical care may be used to satisfy the screening requirements, provided that informed consent for the use of these data was obtained and the evaluations took place within the required timeframe.

Table 1. Phase 1 Screening Assessments

Assessment	Up to 72 Hours Before Enrollment	Up to 7 Days Before Enrollment
Complete history and physical examination	X	
Bone marrow aspirate		X[a]
Lumbar puncture		X
Examination for testicular involvement		X
ECG (12-lead)		X
Echocardiogram (fractional shortening)		X
Local laboratory evaluations:		
CBC with differential and platelet count	X	
Serum electrolytes: Na, K, Cl, CO_2, Ca, Mg, P	X	
Blood glucose	X	
Renal function: BUN, Cr; NM-GFR only if Cr ≥1.5 x ULN	X	
Hepatic function: AST, ALT, total and direct bilirubin, ALP, albumin	X	
Pancreatic function: amylase, lipase	X	
Uric acid	X	
Serum or urine pregnancy test, FCBP	X	
Hepatitis B testing		X[b]

ALP = alkaline phosphatase; ALT = alanine aminotransferase; anti-HBs = hepatitis B surface antibody; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; Cr = serum creatinine; ECG = electrocardiogram; FCBP = female of childbearing potential; HBV = hepatitis B virus; NM-GFR = nuclear magnetic-glomerular filtration rate; ULN = upper limit of normal.

[redacted]

[b] Hepatitis serologies may be obtained up to 2 weeks prior to enrollment. Testing is not required if tested negative within 6 months of screening and no change in the subject's risk factors within these 6 months. Subjects with positive testing or a history of prior hepatitis B virus (HBV) infection should have consultation with a specialist and must have HBV-DNA testing at screening and again at safety follow up. Subjects that have received hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV-DNA monitoring.

Physical Examination

A complete history and physical examination must include all of the following:

- Review of medical and surgical histories, including:
  - Prior cumulative anthracycline exposure (refer to Appendix G, Guidance for Determining Previous Cumulative Anthracycline Dose)
  - Known or suspected cancer predisposition syndromes

  - Other co-morbidities which, in the investigator's opinion, either place a subject at increased risk for AEs, or have potential impact on the results of study-specified tests. This includes, but is not limited to:
    - Endocrinopathies
    - Gastrointestinal disorders
    - Inborn errors of metabolism
    - Congenital heart disease, repaired or unrepaired
    - Epilepsy
  - Documentation of all current medications
- Vital signs:
  - Temperature
  - Heart rate
  - Respiratory rate
  - Systolic and diastolic blood pressures
- Weight, height, and BSA
- Performance status assessment (Appendix F):
  - Lansky score if $<$ 16 years of age
  - Karnofsky score if $\geq$ 16 years of age
- Examination of all of the following:
  - Head
  - Ears
  - Eyes
  - Nose
  - Oropharynx
  - Neck
  - Heart
  - Lungs
  - Abdomen
  - Genitalia
  - Back
  - Extremities
  - Lymph nodes
  - Skin
  - Nervous system
- Determination of the baseline NCI-CTCAE (Version 4.03) grade for all abnormal physical examination findings

Bone Marrow Aspirate

Bone marrow aspirate must be obtained and a morphologic diagnosis of relapsed or refractory ALL must be determined prior to study enrollment. In the event that aspirate cannot be obtained, diagnosis may be made by biopsy. It is not necessary for the results of immunophenotyping or cytogenetic studies to be available prior to enrollment or the initiation of study treatment. Bone marrow status definitions are provided in Table 2.

A portion of the bone marrow obtained during screening will be submitted to a central laboratory to facilitate the analysis of MRD. Peripheral blood may be obtained prior to treatment and submitted in its place, only for subjects from whom sufficient bone marrow could not be obtained. Instructions for the collection and submission of MRD specimens are provided in the Laboratory Manual.

Note: Although not part of the screening assessment, a sample for [redacted] must be obtained at the time of the diagnostic bone marrow aspirate for subjects from whom consent for these optional studies has been obtained.

Table 2. Phase 1 and 2 Bone Marrow Status Definitions

Status Level	Description
M1 Marrow	Less than 5% blasts in a bone marrow aspirate and at least 200 cells counted
M2 Marrow	5%–25% blasts in a bone marrow aspirate with at least 200 cells counted
M3 Marrow	Greater than 25% blasts in a bone marrow aspirate with at least 200 cells counted

Lumbar Puncture

Cerebrospinal fluid must be obtained prior to the initiation of study treatment and examination must include:

- Red blood cell (RBC) count
- White blood cell (WBC) count
- Differential
- Cytology

It is not necessary for central nervous system (CNS) status to be declared prior to the initiation of study treatment. CNS status must be declared prior to the second scheduled lumbar puncture, however, as this informs the treatment regimen from that day on. CNS status definitions are provided in Table 3.

Table 3. Phase 1 and 2 CNS Status Definitions

CNS Status Level	Description	
CNS 1	In CSF, absence of blasts on cytospin preparation, regardless of the number of WBCs	
CNS 2	In CSF, presence < 5 mcl WBCs and cytospin positive for blasts, or ≥ 5 mcl WBCs but negative by Steinherz/Bleyer algorithm[a]:	
	CNS 2a	< 10 mcl RBCs; < 5 mcl WBCs and cytospin positive for blasts
	CNS 2b	≥ 10 mcl RBCs; < 5 mcl WBCs and cytospin positive for blasts
	CNS 2c	≥ 10 mcl RBCs; ≥ 5 mcl WBCs and cytospin positive for blasts but negative by Steinherz/Bleyer algorithm[a]
CNS 3	In CSF, presence of ≥ 5/μL WBCs and cytospin positive for blasts and/or clinical signs of CNS leukemia:	
	CNS 3a	< 10 mcl RBCs; ≥ 5 mcl WBCs and cytospin positive for blasts
	CNS 3b	≥ 10 mcl RBCs, ≥ 5 mcl WBCs and positive by Steinherz/Bleyer algorithm[a]
	CNS 3c	Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome)

CNS = central nervous system; CSF = cerebrospinal fluid; RBC = red blood cell; WBC = white blood cell.

[a] If the subject has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5 WBC/mcl and blasts, the following Steinherz/Bleyer algorithm should be used to distinguish between CNS2 and CNS3 disease: $\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2\text{X} \frac{\text{Blood WBC}}{\text{Blood RBC}}$

Subjects with CNS 3 leukemia will be considered to be CNS-positive throughout this study. All other subjects are considered to be CNS-negative.

The first dose of intrathecal (IT) chemotherapy may be given with the diagnostic lumbar puncture, in accordance with institutional practice, and is considered to be part of Day 1 study treatment, provided that study enrollment and the remainder of Day 1 study treatment occur within the required timeframe.

A single-page screening assessments reference is provided in Appendix A.

8. Dosage and Treatment Administration

The phase 2 protocol, including details on phase 2 dose and treatment administration are provided in Appendix K.

Study treatment should be initiated within approximately 48 hours after enrollment. The Sponsor study medical monitor should be contacted if circumstances prevent this.

A ± 1-day window is permitted for the delivery of all scheduled study treatments. Other backbone chemotherapy and assessments may be aligned with carfilzomib based on investigator discretion.

8.1 Treatment Administration

8.1.1 Carfilzomib Single-agent Lead-in Window (Dose Escalation 1 [R3] Only)

During the Dose Escalation 1 (R3) portion of the study only, the Induction Cycle will be preceded by a 1-week carfilzomib single-agent Lead-in Window. The schedule of treatment and response assessments for the Lead-in Window is presented in Table 4.

Table 4. Phase 1 Schedule of Treatment and Response Assessments, Lead-in Window

Study Drug	Cycle Days		
	1	2	8
Systemic Treatment			
Carfilzomib	X	X	
Premedication with dexamethasone	X	X	
Prehydration	X	X	
CNS Treatment			
Chemotherapy with Diagnostic Lumbar Puncture[a]	X		
Response Assessment			X

Note: Lead-in Window will only occur in the Dose Escalation 1 (R3) portion of the study.
[a] Intrathecal chemotherapy per institutional practice; may include cytarabine, methotrexate, or triple therapy (cytarabine, hydrocortisone, and methotrexate).

Carfilzomib

Carfilzomib will be given as an IV infusion over approximately 30 (± 5) minutes on Days 1 and 2 of the carfilzomib single-agent Lead-in Window. Subjects in all cohorts will receive 20 mg/m^2 of carfilzomib on Day 1 of the Lead-in Window; the Day 2 carfilzomib infusions will be given at the assigned dose level for each cohort:

- Dose Level 1: 20 mg/m^2
- Dose Level 2: 27 mg/m^2
- Dose Level 3: 36 mg/m^2
- Dose Level 4: 45 mg/m^2

Subjects with a BSA > 2.2 m^2 will receive a dose calculated based on a BSA of 2.2 m^2. Premedication with 3 mg/m^2 of dexamethasone (oral or IV) will be administered approximately 30 minutes prior to the start of each carfilzomib infusion.

Adequate hydration is required to mitigate the risks for TLS and pre-renal azotemia, which have been associated with carfilzomib. Prehydration with at least 125 mL/m^2/hour of IV fluid is required for 1 hour prior to carfilzomib administration; hydration management is otherwise at the investigator's discretion and should be appropriate for the clinical situation. Detailed supportive care guidelines regarding TLS are provided in Section 9.1.

Central Nervous System Treatment (According to age-based dosing presented in Table 6)

Preservative-free forms of cytarabine, hydrocortisone, and methotrexate should be used for IT administration.

- Intrathecal chemotherapy in accordance with institutional practice given within 7 days before enrollment or on Day 1

Disease Progression During the Carfilzomib Single-agent Lead-in Window

If the subject has a greater than 25% increase in circulating blasts during the carfilzomib single-agent Lead-in Window and the investigator deems them no longer suitable for single-agent therapy, the subject will be advanced to Day 1 of the Induction Cycle and will begin combination chemotherapy. Should this occur, Days 1 and 2 carfilzomib doses during the Induction Cycle will be eliminated and the subject will receive 6, rather than 8, total doses of carfilzomib prior to the end-of-induction response assessment.

8.1.2 Induction (Dose Escalation 1 [R3] and Dose Escalation 2 [VXLD])

The Induction Cycle consists of a 4-week cycle of treatment that includes carfilzomib and a combination chemotherapy backbone (R3 in Dose Escalation 1 or VXLD in Dose Escalation 2). During the Dose Escalation 1 portion of the study, the Induction Cycle begins on Day 8 of the carfilzomib single-agent Lead-in Window and there are no minimum blood cell count requirements in order to begin. During the Dose Escalation 2 portion of the study, induction is the first cycle of therapy that the subject will receive.

The schedule of treatment and response assessments for the Induction Cycle is presented in Table 5. Induction Cycle Road Maps for Dose Escalation 1 and Dose Escalation 2 are provided in Figure 2 and Figure 3 respectively.

Table 5. Phase 1 Schedule of Treatment and Response Assessments, Induction Cycle

Study Drug	Cycle Days																											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**
Systemic Treatment																													
Investigational Drug																													
Carfilzomib[a]	X	X						X	X						X	X													
Premedication with dexamethasone								X	X																				
Prehydration	X	X						X	X						X	X													
R3 Chemotherapy Backbone (Dose Escalation 1)																													
Dexamethasone	X	X	X	X	X										X	X	X	X	X										
Mitoxantrone	X	X																											
PEG-asparaginase			X															X											
Vincristine			X							X							X							X					
VXLD Chemotherapy Backbone (Dose Escalation 2)																													
Daunorubicin	X							X							X							X						
Dexamethasone	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								
PEG-asparaginase				X														X											
Vincristine	X							X							X							X						

Footnotes defined on next page

Table 5. Phase 1 Schedule of Treatment and Response Assessments, Induction Cycle

Study Drug	Cycle Days																												
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
CNS Treatment																													
Chemotherapy with Diagnostic Lumbar Puncture[b]																													
Dose Escalation 1 (R3)																													
Dose Escalation 2 (VXLD)	X																												
IT Methotrexate (CNS-negative)																													
Dose Escalation 1 (R3)	X																												
Dose Escalation 2 (VXLD)								X																					
IT Triple Therapy[c] (CNS-positive)																													
Dose Escalation 1 (R3)	X							X							X														X
Dose Escalation 2 (VXLD)								X							X							X						X
Response Assessment																													X

CNS = central nervous system; IT = intrathecal; PEG = polyethylene glycol.

[a] For dose escalation 2 (VXLD) carfilzomib administration may be within ± 1 days for each scheduled dose. Other backbone chemotherapy and assessments may be aligned with carfilzomib based on investigator discretion.

[b] Intrathecal chemotherapy per institutional practice; may include cytarabine, methotrexate, or triple therapy (cytarabine, hydrocortisone, and methotrexate).

[c] Triple therapy comprises cytarabine, hydrocortisone, and methotrexate.

8.1.2.1 Dose Escalation 1 (R3)

Carfilzomib

Carfilzomib will be given as an intravenous infusion over 30 ± 5 minutes on Days 1, 2, 8, 9, 15, and 16 of the Induction Cycle. Subjects with a BSA > 2.2 m^2 will receive a dose calculated based on a BSA of 2.2 m^2. On the days on which the treatment regimen includes carfilzomib, but not dexamethasone (Days 8 and 9 of the Induction Cycle of Dose Escalation 1 [R3]), premedication with 3 mg/m^2 of dexamethasone (oral or IV) will be administered approximately 30 minutes prior to the start of the carfilzomib infusion.

Adequate hydration is required to mitigate the risks for TLS and pre-renal azotemia, which have been associated with carfilzomib. Prehydration with at least 125 mL/m^2/h of IV fluid is required for 1 hour prior to carfilzomib administration; hydration management is otherwise at the investigator's discretion and should be appropriate for the clinical situation. Detailed supportive care guidelines regarding TLS are provided in Section 9.1.

During Dose Escalation 1 (R3), carfilzomib infusions will be given at the assigned dose level for each cohort:

- Dose Level 1: 20 mg/m^2
- Dose Level 2: 27 mg/m^2
- Dose Level 3: 36 mg/m^2
- Dose Level 4: 45 mg/m^2

Induction Chemotherapy Backbone for Dose Escalation 1 (R3)

- Dexamethasone 10 mg/m^2 given orally twice daily on Days 1–5 and 15–19
  - IV administration is acceptable, if the subject is unable to tolerate oral administration.
  - Round the calculated dosage up to the nearest one-half tablet or 0.1 mL.
- Mitoxantrone, 10 mg/m^2 IV on Days 1 and 2
  - Infuse over 10−15 minutes in 5% Dextrose Injection, USP (D5W)
- PEG-asparaginase 1000 U/m^2 IV on Days 3 and 18
  - Infuse over 1–2 hours in D5W or normal saline.
  - Rapid access to emergency medications (ie, epinephrine and methylprednisolone) during and for approximately 24 hours following dosage administration is strongly recommended.
  - See Section 8.4.9 for information regarding the substitution of Erwinia for PEG-asparaginase.
- Vincristine 1.5 mg/m^2 (maximum 2-mg dose) IV on Days 3, 10, 17, and 24
  - Administer as an IV push over 1 minute or as an infusion, in accordance with institutional practice.

8.1.2.2 Dose Escalation 2 (VXLD)

Carfilzomib

Carfilzomib will be dosed twice weekly over 30 ± 5 minutes, on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. Subjects with a BSA > 2.2 m^2 will receive a dose calculated based on a BSA of 2.2 m^2. The administration may be within ± 1 days for each scheduled dose. Adequate hydration is required to mitigate the risks for TLS and pre-renal azotemia, which have been associated with carfilzomib. Prehydration with at least 125 mL/m^2/h of IV fluid is required for 1 hour prior to carfilzomib administration; hydration management is otherwise at the investigator's discretion and should be appropriate for the clinical situation. Detailed supportive care guidelines regarding TLS are provided in Section 9.1.

During Dose Escalation 2 (VXLD), subjects will receive 20 mg/m^2 of carfilzomib on Day 1 of the Induction Cycle. From Day 2 of the Induction Cycle on, carfilzomib will be infused at the assigned dose level for each cohort:

- Dose Level 2: 27 mg/m^2
- Dose Level 3: 36 mg/m^2
- Dose Level 4: 45 mg/m^2
- Dose Level 5: 56 mg/m^2
- Dose Level 6: 70 mg/m^2

Induction Chemotherapy Backbone for Dose Escalation 2 (VXLD)

For phase 2 (Appendix K), the dose of daunorubincin has been adjusted and acceptable substitutions for components of VXLD have been incorporated based on local availability and standard practice. In addition, a separate VXLD schedule is provided for infants. Section 22.1.2 provides details for the backbone dose and schedule for children ≥ 12 months and for infants < 12 months (see also Table 15 and Table 17, respectively).

Backbone therapy for phase 1 is described below. If carfilzomib window is adjusted, scheduled backbone therapy may be adjusted ± 1 day to align with carfilzomib at investigator's discretion.

- Daunorubicin, 25 mg/m^2 IV on Days 1, 8, 15, and 22
  - Administer into a large vein as an IV push or as an infusion over 1-15 minutes, or longer as required by institutional practice.
  - Administration in conjunction with rapidly infusing D5W or normal saline is recommended.
  - Protect from sunlight.

- Dexamethasone 6 mg/m^2 per day BID - given orally (3 mg/m^2 per dose given twice daily) on Days 1-21
  - IV administration is acceptable, if the subject is unable to tolerate oral administration.
  - Round the calculated dosage up to the nearest one-half tablet or 0.1 mL.
- PEG-asparaginase 2500 U/m^2 IV on Days 4 and 18
  - Infuse over 1–2 hours in D5W or normal saline.
  - Rapid access to emergency medications (ie, epinephrine and methylprednisolone) during and for approximately 24 hours following dosage administration is strongly recommended.
  - See Section 8.4.9 for information regarding the substitution of Erwinia for PEG-asparaginase.
- Vincristine 1.5 mg/m^2 (maximum 2-mg dose) IV on Days 1, 8, 15, and 22
  - Administer as an IV push over 1 minute or as an infusion, in accordance with institutional practice.

CNS Treatment (According to age-based dosing presented in Table 6)

Preservative-free forms of cytarabine, hydrocortisone, and methotrexate should be used for intrathecal administration.

- *CNS Treatment for Dose Escalation 1 (R3):*
  - CNS-negative subjects: IT methotrexate given on Day 1
  - CNS-positive subjects: IT Triple Therapy (cytarabine, hydrocortisone, and methotrexate) given on Days 1, 8, 15, and 29
- *CNS Treatment for Dose Escalation 2 (VXLD):*
  - Intrathecal (IT) chemotherapy in accordance with institutional practice given within 7 days before enrollment or on Day 1
  - CNS-negative subjects: IT methotrexate given on Day 8
  - CNS-positive subjects: IT Triple Therapy (cytarabine, hydrocortisone, and methotrexate) given on Days 8, 15, 22, and 29

Table 6. Phase 1 and 2 Age-based Dosing Guidelines

	Dose		
Age (years)	**Cytarabine (mg)**	**Hydrocortisone (mg)**	**Methotrexate (mg)**
1 to 1.99	16	8	8
2 to 2.99	20	10	10
3 to 8.99	24	12	12
≥ 9	30	15	15

Figure 2. Study 20140106 Road Map, Induction Cycle, Dose Escalation 1 (R3)

Section 8.1.2 Induction Cycle (Dose Escalation 1 [R3]) The Induction Cycle lasts for 4 weeks	_____ **Patient name or initials**	_____ **DOB**

Drug	**Route**	**Dosage**	**Days**	**Important notes**
Methotrexate (MTX) (CNS negative)	IT	Age-based dosing (see table below)	Day 1	
IT Triple Therapy (ITT) (CNS positive)	IT	**Age-based dosing:** **Age (yrs) / ARAC / HC / MTX** 1 to 1.99 / 16 / 8 / 8 2 to 2.99 / 20 / 10 / 10 3 to 8.99 / 24 / 12 / 12 ≥ 9 / 30 / 15 / 15	Days 1, 8, 15, 29	IT Triple Therapy comprises: cytarabine (ARAC) hydrocortisone (HC) methotrexate (MTX)
Carfilzomib (CFZ)	IV over 30 ± 5 min	Dose Level 1: 20 mg/ m^2 Dose Level 2: 27 mg/ m^2 Dose Level 3: 36 mg/ m^2 Dose Level 4: 45 mg/ m^2	Days 1, 2, 8, 9, 15, 16	Prehydrate with 125 mL/ m^2/hour x 1 hour prior to CFZ. Premedicate with 3 mg/ m^2 of Dex (oral or IV) ~ 30 minutes prior to CFZ on Days 8 and 9 only. If BSA > 2.2 m^2, base dose on a BSA of 2.2 m^2.
Dexamethasone (Dex)	PO, IV	10 mg/m^2, twice daily	Days 1–5, 15–19	Round the calculated dosage up to the nearest ½ tablet or 0.1 mL.
Mitoxantrone (Mito)	IV over 10–15 min	10 mg/ m^2	Days 1, 2	
PEG-asparaginase(PEG)	IV over 1–2 hours	1000 U/ m^2	Days 3, 18	Rapid access to emergency medications (ie, epinephrine and methylprednisolone) for ~24 hours following dosage administration is strongly recommended.
Vincristine (VCR)	IV push over 1 min	1.5 mg/ m^2	Days 3, 10, 17, 24	2 mg maximum dose. Administration by infusion is acceptable.

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Study Day	CFZ ____mg	Dex ____mg	Mito ____mg	PEG ____U	VCR ____mg	Complete as applicable: IT MTX ____mg	Complete as applicable: ITT __mg/__mg/__mg ARAC/HC/MTX	Comments (include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below.							
		1	____mg	_____mg _____mg	____mg			____mg	ARAC ____mg HC ____mg MTX ____mg	
		2	____mg	_____mg _____mg	____mg					
		3		_____mg _____mg		____U	____mg			
		4		_____mg mg						
		5		_____mg _____mg						
		8	____mg						ARAC ____mg HC ____mg MTX ____mg	
		9	____mg							
		10					____mg			
		15	____mg	_____mg _____mg					ARAC ____mg HC ____mg MTX mg	
		16	____mg	_____mg _____mg						
		17		_____mg _____mg			____mg			
		18		_____mg _____mg		____U				
		19		_____mg _____mg						
		24					____mg			
		29							ARAC ____mg HC ____mg MTX ____mg	
			DOSE MODIFICATION GUIDELINES are provided in Section 8.4. If stable disease or better response is achieved at the end of the Induction Cycle, patients have the opportunity to participate in the Optional Consolidation Cycle. A new Informed Consent Form, and pediatric assent (when applicable), must be obtained.							

Figure 3. Study 20140106 Road Map, Induction Cycle, Dose Escalation 2 (VXLD)

Section 8.1.2 Induction Cycle (Dose Escalation 2 [VXLD]) The Induction Cycle lasts for 4 weeks	_____ **Patient name or initials**	_____ **DOB**

Drug	Route	Dosage	Days	Important notes
Initial IT Chemotherapy	IT	Age-based dosing (see table below) or per institutional guidelines	Day 1 or with diagnostic LP	May include MTX, ITT, or ARAC.
Methotrexate (MTX) (CNS negative)	IT	Age-based dosing (see table below)	Day 8	
IT Triple Therapy (ITT) (CNS positive)	IT	**Age-based dosing:** **Age (yrs) ARAC HC MTX** 1 to 1.99 16 8 8 2 to 2.99 20 10 10 3 to 8.99 24 12 12 ≥ 9 30 15 15	Days 8, 15, 22, 29	IT Triple Therapy comprises: cytarabine (ARAC) hydrocortisone (HC) methotrexate (MTX)
Carfilzomib (CFZ)	IV over 30 ± 5 min	20 mg/m^2	Day 1	Prehydrate with 125 mL/m^2/hour x 1 hour prior to CFZ. If BSA > 2.2 m^2, base dose on a BSA of 2.2 m^2. Administration may be within ± 1 days for each scheduled dose. Other backbone chemotherapy and assessments may be aligned with carfilzomib based on investigator discretion.
		Dose Level 2: 27 mg/ m^2 Dose Level 3: 36 mg/ m^2 Dose Level 4: 45 mg/ m^2 Dose Level 5: 56 mg/m^2 Dose Level 6: 70 mg/m^2	Days 2, 8, 9, 15, 16	
Daunorubicin (DNR)	IV over 1–15 min	25 mg/m^2	Days 1, 8, 15, and 22	Administration in conjunction with rapidly infusing D5W or normal saline is recommended. Protect from sunlight.
Dexamethasone (Dex)	PO, IV	6 mg/m^2 per day BID (3 mg/m^2 per dose given twice daily)	Days 1–21	Round the calculated dosage up to the nearest ½ tablet or 0.1 mL.
PEG-asparaginase(PEG)	IV over 1–2 hours	2500 U/m^2	Days 4, 18	Rapid access to emergency medications (ie, epinephrine and methylprednisolone) for approximately 24 hours following dosage administration is strongly recommended.
Vincristine (VCR)	IV push over 1 min	1.5 mg/m^2	Days 1, 8, 15, 22	2 mg maximum dose. Administration by infusion is acceptable.

Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Study Day	CFZ Day 1 ____mg Days 2 onward ____mg	Dex ____mg	DNR ____mg	PEG ____U	VCR ____mg	Complete as applicable: IT MTX ____mg	Complete as applicable: ITT __mg/__mg/__mg ARAC/HC/MTX	Complete as applicable: IT ARAC _____mg	Comments (include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below								
		1	____mg	_____mg _____mg	____mg		____mg	____mg	ARAC ____mg HC ____mg MTX ____mg	____mg	_____ Date first IT chemotherapy given
		2	____mg	_____mg _____mg							
		3		_____mg _____mg							
		4		_____mg _____mg		____U					
		5		_____mg _____mg							
		6		_____mg _____mg							
		7		_____mg _____mg							
		8	____mg	_____mg _____mg	____mg		____mg	____mg	ARAC ____mg HC ____mg MTX ____mg		
		9	____mg	_____mg _____mg							
		10		_____mg _____mg							
		11		_____mg _____mg							
		12		_____mg _____mg							
		13		_____mg _____mg							
		14		_____mg _____mg							

Date Due	Date Given	Study Day	CFZ Day 1 ____mg Days 2 onward ____mg	Dex ____mg	DNR ____mg	PEG ____U	VCR ____mg	Complete as applicable			Comments (include any held doses, or dose modifications)
								IT MTX ____mg	ITT __mg/__mg/__mg ARAC/HC/MTX	IT ARAC _____mg	
		15	____mg	_____mg _____mg	____mg		____mg		ARAC ____mg HC ____mg MTX ____mg		
		16	____mg	_____mg _____mg							
		17		_____mg _____mg							
		18		_____mg _____mg		____U					
		19		_____mg _____mg							
		20		_____mg _____mg							
		21		_____mg _____mg							
		22			____mg		____mg		ARAC ____mg HC ____mg MTX ____mg		
		24									
		29							ARAC ____mg HC mg MTX ____mg		
			DOSE MODIFICATION GUIDELINES are provided in Section 8.4. If stable disease or better response is achieved at the end of the Induction Cycle, patients have the opportunity to participate in the Optional Consolidation Cycle. A new Informed Consent Form, and pediatric assent (when applicable), must be obtained.								

8.1.3 Optional Consolidation

Subjects with SD or better response at the end of the Induction Cycle will be offered an optional cycle of consolidation chemotherapy. A new ICF and, where applicable, a new pediatric assent form will be required.

The Optional Consolidation Cycle begins on Day 36 of the Induction Cycle (7 days after the Day 29 response assessment) or when absolute neutrophil count (ANC) is $>$ 750/mcl and platelet count is $>$ 75,000/mcl, whichever comes later. Subjects with SD, partial response (PR), CRp, or complete remission with incomplete hematologic recovery (CRi) at the end of the Induction Cycle who are not expected to fully recover their blood counts may begin the optional cycle of consolidation on Day 36 of the Induction Cycle.

The Optional Consolidation Cycle is composed of a single 4-week cycle of carfilzomib in combination with a Children's Oncology Group (COG)-modified Berlin-Frankfurt-Münster (BFM) chemotherapy backbone (6-mercaptopurine, cyclophosphamide, cytarabine, PEG-asparaginase, vincristine), and appropriate CNS therapy administered according to the schedule of treatment and response assessments presented in Table 7.

All drugs in the optional consolidation treatment regimen should be dosed based on weight, height, and BSA determined within 7 days of the start of the cycle.

The Optional Consolidation Cycle Road Map is provided in Figure 4.

Table 7. Phase 1 Schedule of Treatment and Response Assessment, Optional Consolidation Cycle

Event	Cycle Days																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	22	29
Systemic treatment																		
Investigational Drug																		
Carfilzomib	X	X						X	X						X	X		
Premedication with dexamethasone	X	X						X	X						X	X		
Chemotherapy Backbone																		
6-mercaptopurine	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Cyclophosphamide	X																	
Cytarabine	X	X	X	X				X	X	X	X							
PEG-asparaginase															X			
Vincristine															X		X	
CNS treatment																		
IT Methotrexate (CNS-negative)	X							X							X		X	
IT Triple Therapy[a] (CNS-positive)	X							X							X		X	
Response assessment																		X

CNS = central nervous system; IT = intrathecal; PEG = polyethylene glycol.
[a] Triple therapy comprises cytarabine, hydrocortisone, and methotrexate.

Carfilzomib

In phase 2 (Appendix K), consolidation for children ≥ 12 months will follow the structure below and is detailed in Table 19. For infants < 12 months, the consolidation dose and schedule is detailed in Table 21. Permitted substitutions are listed in Section 22.1.2.1.

Subjects who participate in the Optional Consolidation Cycle will receive carfilzomib as an IV infusion over 30 ± 5 minutes on Days 1, 2, 8, 9, 15, and 16. Carfilzomib will be administered at the same dose level to which the subject was assigned during the Lead-in Window and/or Induction Cycle. Subjects with a BSA > 2.2 m^2 will receive a dose calculated based on a BSA of 2.2 m^2. For subjects in dose escalation 2 (VXLD) carfilzomib administration may be within ± 1 days for each scheduled dose. Premedication with 3 mg/m^2 of dexamethasone (oral or IV) will be administered 30 minutes prior to the start of each carfilzomib infusion.

Prehydration is not required during the Optional Consolidation Cycle unless the subject remains at risk for TLS.

Consolidation Backbone

- 6-mercaptopurine, 60 mg/m^2 given orally on Days 1 to 14
  - Actual dose per day should be varied, as needed, to yield a weekly dose as close to 420 mg/m^2 as possible.
  - See Section 8.4.2 for management of subjects with thiopurine methyltransferase (TPMT) polymorphisms.
  - Enteral administration is acceptable if the subject is unable to tolerate oral administration.
  - Administer at least 1 hour before and 2 hours after intake of food or drink, except for water.
- Cyclophosphamide 1000 mg/m^2 IV on Day 1
  - Infuse over 30 to 60 minutes.
  - There are no requirements for hydration or mesna administration, unless the subject has a history of hematuria; see Section 8.4.3.
- Cytarabine 75 mg/m^2 IV or subcutaneously on Days 1 to 4 and 8 to 11
  - IV administration should be infused over 1 to 30 minutes.
  - Subcutaneous administration sites should be rotated among the thighs, abdomen, and flanks.
- PEG-asparaginase 1000 U/m^2 IV on Day 15
  - Infuse over 1 to 2 hours in D5W or normal saline.
  - Rapid access to emergency medications (ie, epinephrine and methylprednisolone) during and for approximately 24 hours following dose administration is strongly recommended.
  - See Section 8.4.9 for information regarding the substitution of Erwinia for PEG-asparaginase.
- Vincristine 1.5 mg/m^2 (maximum 2 mg per dose) IV on Days 15 and 22
  - Administer as an IV push over 1 minute or as an infusion, in accordance with institutional practice.

CNS Treatment (According to age-based dosing presented in Table 6)

Preservative free forms of cytarabine, hydrocortisone, and methotrexate should be used for intrathecal administration.

- CNS-negative subjects: IT methotrexate given on Days 1, 8, 15, and 22
- CNS-positive subjects: IT Triple Therapy (cytarabine, hydrocortisone, and methotrexate) given on Days 1, 8, 15, and 22

Figure 4. Study 20140106 Road Map, Optional Consolidation Cycle

Section 8.1.3 Optional Consolidation Cycle The Optional Consolidation Cycle lasts for 4 weeks	_____ Patient name or initials	_____ DOB

Drug	Route	Dosage	Days	Important notes
Methotrexate (MTX) (CNS negative)	IT	Age-based dosing (see table below)	Days 1, 8, 15, 22	
IT Triple Therapy (ITT) (CNS positive)	IT	Age-based dosing: Age (yrs) ARAC HC MTX 1 to 1.99 16 8 8 2 to 2.99 20 10 10 3 to 8.99 24 12 12 ≥ 9 30 15 15	Days 1, 8, 15, 22	IT Triple Therapy comprises: cytarabine (ARAC) hydrocortisone (HC) methotrexate (MTX)
Carfilzomib (CFZ)	IV over 30 ± 5 min	Patients to receive dose level to which they were assigned during the Lead-in Window and/or Induction Cycle	Days 1, 2, 8, 9, 15, 16	Premedicate with 3 mg/m^2 of Dex (oral or IV) ~ 30 minutes prior to each CFZ dose. If BSA > 2.2 m^2, base dose on a BSA of 2.2 m^2.
6-mercaptopurine (6-MP)	PO	60 mg/m^2	Days 1–14	Administer on an empty stomach. Actual dose per day should be varied, as needed, to yield a weekly dose as close to 420 mg/m^2 as possible.
Cyclophosphamide (CPM)	IV over 30–60 min	1000 mg/m^2	Day 1	
Cytarabine (ARAC)	IV over 1–30 min or SC	75 mg/m^2	Days 1–4, 8–11	
PEG-asparaginase(PEG)	IV over 1–2 hours	1000 U/m^2	Day 15	Rapid access to emergency medications (ie, epinephrine and methylprednisolone) for approximately 24 hours following dosage administration is strongly recommended.
Vincristine (VCR)	IV push over 1 min	1.5 mg/m^2	Days 15, 22	2 mg maximum dose. Administration by infusion is acceptable.

Ht_____cm Wt_____kg BSA_____m^2

*	Date Given	Study Day	CFZ ____mg	6-MP ____mg	CPM ____mg	ARAC ____mg	PEG ____U	VCR ____mg	Complete as applicable: IT MTX ____mg	Complete as applicable: ITT __mg/__mg/__mg ARAC/ HC / MTX	Comments (include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below								
		1	____mg	____mg	____mg	____mg			____mg	ARAC ____mg HC ____mg MTX ____mg	
		2	____mg	____mg		____mg					
		3		____mg		____mg					
		4		____mg		____mg					
		5		____mg							
		6		____mg							
		7		____mg							
		8	____mg	____mg		____mg			____mg	ARAC ____mg HC ____mg MTX ____mg	
		9	____mg	____mg		____mg					
		10		____mg		____mg					
		11		____mg		____mg					
		12		____mg							
		13		____mg							
		14		____mg							
		15	____mg				____U	____mg	____mg	ARAC ____mg HC ____mg MTX ____mg	
		16	____mg								
		22						____mg	____mg	ARAC ____mg HC ____mg MTX ____mg	
			DOSE MODIFICATION GUIDELINES are provided in Section 8.4.								

8.1.4 Testicular Relapse

The management of testicular relapse is at the investigator's discretion, however, radiotherapy may not be administered concurrent with participation in this study.

8.2 Dose-limiting Toxicity

Carfilzomib will be immediately omitted for any DLT. Subjects may continue with the remainder of the backbone therapy, at the investigator's discretion, should this occur. Carfilzomib may be reintroduced at a lower dose, in accordance with the information presented in Section 8.4.1. If carfilzomib is not reintroduced, the subject is considered to be withdrawn from study treatment.

Subjects who discontinue treatment, receive a dose modification, or miss doses of carfilzomib because of a non-dose-limiting toxicity adverse event or deviation from the protocol will be replaced.

8.3 Definition of Carfilzomib Dose-limiting Toxicity

A DLT is defined as any of the following toxicities assessed by the investigator as possibly, probably, or definitely attributable to carfilzomib during the Lead-in Window or Induction Cycle:

- Any Grade 4 nonhematologic toxicity, excluding:
  - Alopecia
  - Infection
  - TLS
  - Fever and neutropenia
  - Fatigue
  - Nausea or vomiting
  - Sensory or motor neuropathy or neuropathic pain
  - In the absence of associated clinical and radiological criteria evocative of pancreatitis, Grade 4 laboratory elevation of lipase in the absence of Grade 4 laboratory elevation of amylase or Grade 4 laboratory elevation of amylase in the absence of Grade 4 laboratory elevation of lipase
  - The following, provided there is a return to Grade 1 status or subject's baseline by the time of induction treatment course completion and blood count recovery (no later than Day 42 of the Induction Cycle):
    - Electrolyte abnormalities
    - Hyper- or hypoglycemia
    - Elevations of AST, ALT, gamma-glutamyl transferase (GGT), triglycerides, or bilirubin

- ≥ Grade 4 neutropenia or ≥ Grade 3 thrombocytopenia persisting beyond Day 45 (Day 42 prior to Protocol Amendment 3) of the Induction Cycle in a subject who otherwise has a CR

Serious adverse events and grade 4 adverse events considered unrelated or unlikely to be related to carfilzomib are not considered DLTs and do not require stopping carfilzomib. If carfilzomib is temporarily stopped for an event that the investigator does not attribute to carfilzomib, it may be resumed within the allowed administration window, at the previous dose, based on the investigators risk benefit assessment.

8.4 Dose-modification Guidelines

8.4.1 Carfilzomib

The dose decrements for carfilzomib are presented in Table 8.

Carfilzomib must be permanently discontinued for subjects requiring more than 1 dose level reduction.

Table 8. Phase 1 and 2 Dose Decrements for Carfilzomib

Original Carfilzomib Dose	Reduced Carfilzomib Dose
20 mg/m^2	15 mg/m^2
27 mg/m^2	20 mg/m^2
36 mg/m^2	27 mg/m^2
45 mg/m^2	36 mg/m^2
56 mg/m^2	45 mg/m^2
70 mg/m^2	56 mg/m^2

The following dose modifications are required for subjects who experience a DLT during the Lead-in or Induction Cycles. For subjects who continue on to the Optional Consolidation Cycle, these same requirements must be applied for any subject who experiences a toxicity that would have been defined as dose limiting, had it occurred during the earlier cycles.

See Section 8.3 for the definition of DLT.

- Omit until improved to ≤ Grade 2 status
- Resume at a reduced dose level according to Table 8 at the investigator's discretion
  - If the investigator determines that reintroducing carfilzomib therapy is not in the subject's best interest, the subject will be considered withdrawn from study treatment.
  - If the toxicity recurs, discontinue carfilzomib treatment

- Subjects continuing on to the Optional Consolidation Cycle may be re-challenged with their original dose of carfilzomib at the investigator's discretion
    - If the toxicity recurs after the subject is re-challenged, omit until improved to ≤ Grade 2 status and then resume at the reduced dose

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES), formerly termed reversible posterior leukoencephalopathy syndrome (RPLS), is a neurological disorder, which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro-radiological imaging. Cases of PRES have been reported in patients receiving carfilzomib. Discontinue carfilzomib if PRES is suspected. The safety of reinitiating carfilzomib therapy in patients previously experiencing PRES is not known.

Subjects who are diagnosed with PRES should not be re-challenged with carfilzomib.

8.4.2 6-mercaptopurine

Absolute neutrophil count and cytopenias:

- Do not modify the dose based on ANC.
- Do not modify, delay, or omit doses in response to cytopenias.

Liver Dysfunction:

- Omit if the AST and/or ALT are ≥ 20 x ULN.
- If AST and/or ALT are ≥ 5 x ULN, but < 20 x ULN, measure serum direct bilirubin
- Direct bilirubin > 2 mg/dL (> 34.2 micromol/L): Omit until resolved.
- Direct bilirubin ≤ 2 mg/dL (≤ 34.2 micromol/L): Do not omit.
    - If direct bilirubin is > 2 mg/dL (> 34.2 micromol/L): Omit until resolved, even if AST and ALT are ≤ 5 x ULN.
    - Do not replace missed doses.

TPMT polymorphisms:

- Provide 10% of the dose to subjects with known homozygous activity-reducing polymorphisms of TPMT.
- TPMT genotyping is not required.
- Measurement of TPMT metabolites is not required.

8.4.3 Cyclophosphamide

History of Hematuria:

- Hydrate per institutional practice and document urine specific gravity < 1.010 prior to the dose.
- Provide IV hydration at a rate of 125 mL/m^2/h for 24 hours following the dose.
    - Monitor urine output per institutional guidelines and adjust the rate of hydration as needed to maintain urine output ≥ 3 mL/kg/h.
- Administer 600 mg/m^2 total of mesna on either of the following schedules:
    - 200 mg/m^2 given 15 minutes prior to, or in conjunction with, cyclophosphamide administration, followed by 200 mg/m^2/dose at 4 hours and 8 hours following the start of cyclophosphamide administration,

      OR
    - Continuous administration of 600 mg/m^2/24 h, beginning 15 minutes prior to, or in conjunction with, cyclophosphamide administration.

8.4.4 Cytarabine

Cytarabine Syndrome:

- Administer systemic hydrocortisone or dexamethasone, in accordance with institutional guidelines.
- Withhold for ≥ Grade 3 rash or conjunctivitis.
    - Treat conjunctivitis with dexamethasone ophthalmic drops, in accordance with institutional practice.
    - Resume and make up missed doses, once resolved.
- Withhold for ≥ Grade 3 infection
    - Obtain cultures as appropriate, based on presentation.
    - Provide antimicrobial therapy, as appropriate.
    - Resume and make up missed doses, once resolved.
- Do not withhold for fever in the absence of presumed or proven serious infection.
- Do not withhold for myelosuppression that begins after consolidation therapy has commenced.

8.4.5 Daunorubicin or Other Anthracycline

Cardiac Toxicity

- Discontinue for cardiomyopathy, as defined by LVFS < 27%, LVEF < 50%, or Grade ≥ 3 systolic dysfunction

Extravasation

- Discontinue administration, if extravasation occurs
- Manage the effects of the extravasation per institutional practice

Hyperbilirubinemia

- If direct bilirubin is:
  - ≥ 5.0 mg/dL (> 85.5 micromol/L): Discontinue until resolved
  - 3.1–5.0 mg/dL (51.3–85.5 micromol/L): Give 25% of the dose
  - 1.2–3.0 mg/dL (20.5–51.3 micromol/L): Give 50% of the dose
  - < 1.2 mg/dL (< 20.5 micromol/L): Give the full dose
- Do not make up missed doses

8.4.6 Dexamethasone

Hyperglycemia:

- Do not reduce the dose.
- Insulin therapy may be initiated at the investigator's discretion.

Hypertension:

- Do not reduce the dose.
- Antihypertensive therapy may be initiated at the investigator's discretion.
- Sodium intake may be restricted at the investigator's discretion.

Osteonecrosis:

- Grade 1: Do not reduce the dose.
- Grade 2: Dose modification is permitted at the investigator's discretion.

Pancreatitis:

- Grade 3: Discontinue until resolved.
  - Stress dose steroids may be provided at the investigator's discretion.
- Grade 2: Do not reduce the dose.

Severe infection:

- If steroids need to be discontinued in the opinion of the investigator, it is recommended that the study medical monitor be contacted for discussion before such discontinuation.

Severe psychosis:

- Dose may be reduced by 50% at the investigator's discretion.

8.4.7 Intrathecal Methotrexate or Triple Therapy

Acute neurotoxicity:

- Dose modifications following an acute neurotoxic event are at the investigator's discretion, if thought temporally related to administration of IT methotrexate.
    - Temporally related events commonly occur 9 to 11 days following IT administration.
- Acceptable dose modifications include:
    - Eliminating the next dose
    - Substituting IT cytarabine for the next dose
- Leucovorin or citrovorin may be provided at the investigator's discretion.

Administration via an Ommaya Catheter:

- Give 50% of the age-based dose.

Systemic toxicity:

- Do not reduce the dose.
- Leucovorin or citrovorin may be provided at the investigator's discretion.
    - Do not provide leucovorin or citrovorin without evidence of systemic toxicity.

Viral, bacterial, or fungal meningitis:

- Omit until resolved.
- Do not make up missed doses.

8.4.8 Mitoxantrone

Hyperbilirubinemia:

- If total bilirubin is:
    - $>$ 12 mg/dL ($>$ 205.2 micromol/L): Discontinue until resolved.
    - $>$ 9 mg/dL and $\leq$ 12 mg/dL ($>$ 153.9 micromol/L and $\leq$ 205.2 micromol/L): Give 25% of the dose.
    - $>$ 5 mg/dL and $\leq$ 9 mg/dL ($>$ 85.5 micromol/L and $\leq$ 153.9 micromol/L): Give 50% of dose.
    - $\leq$ 5 mg/dL ($\leq$ 85.5 micromol/L): Give 100% of dose.

8.4.9 PEG-asparaginase or L-asparaginase

$\geq$ Grade 3 Anaphylaxis or $\geq$ Grade 2 Systemic Allergic Reaction:

- Discontinue immediately.
  Manage the reaction in accordance with institutional practice.

- Substitute Erwinia for all future doses.
  If Erwinia is not available, investigators may discontinue asparaginase therapy or consider desensitization procedure acceptable to the site.
- If a subject develops a ≥ Grade 2 allergy to Erwinia asparaginase, discontinue future asparaginase therapy or consider desensitization procedure acceptable to the site.

Given the lack of data available at this time to inform the optimal Erwinia asparaginase schedule, the dose-modification guidelines for ALL trials recommend the substitution or replacement of Erwinia asparaginase for either native or PEG-asparaginase according to the following schedule:

Phase(s) of Treatment	Replacement Schedule for Erwinia asparaginase
Standard Induction, Consolidation, Interim Maintenance, Delayed Intensification.	25,000 IU/m^2/dose IM M/W/F x 6 doses for each dose of pegaspargase.

IM = intramuscular.
NOTES: Should IV administration of Erwinia be approved by the applicable regulatory agency for a site participating in this study, IV administration of Erwinia will be permitted at the investigator's discretion.
If a subject develops a Grade 3 or higher anaphylaxis to Erwinia, discontinue future asparaginase therapy.

Coagulopathy:

- Symptomatic: Discontinue until resolved.
- Asymptomatic: Do not reduce the dose.
- Blood products and/or factor replacement may be provided at the investigator's discretion.
- Hyperbilirubinemia: L-asparaginase may need to be withheld in subjects with an elevated bilirubin, since asparaginase has been associated with hepatic toxicity. No specific guidelines are available.

Hyperglycemia:

- Do not reduce the dose.
- Insulin therapy may be initiated at the investigator's discretion.

Hyperlipidemia:

- Do not reduce the dose.

Intracranial bleed, thrombosis, or infarction:

- Discontinue until resolved.
- Management of the intracranial event is at the investigator's discretion.
- Resume full dose therapy at the investigator's discretion.

Ketoacidosis:

- Discontinue until resolved.
- Management of ketoacidosis is at the investigator's discretion.

Pancreatitis:

- ≥ Grade 3: Discontinue.
  - Do not resume after pancreatitis has resolved.
- Grade 2: Discontinue until resolved.
  - Resume at full dose after pancreatitis has resolved.

Thrombosis:

- Discontinue until resolved.
- Laboratory aberrations without evidence of thrombosis are not an indication for discontinuation.
- Management of thrombosis is at the investigator's discretion.

8.4.10 Vincristine

Constipation, ileus, or typhlitis (≥ Grade 3):

- During the Induction Cycle:
  - Do not reduce or omit the dose.
  - Stool softeners and/or laxatives should be administered to prevent constipation (as described in Section 9.13).
- During the Optional Consolidation Cycle:
  - Discontinue until resolved.
  - Constipation must be treated aggressively, to facilitate ongoing vincristine administration.
  - Resume at 50% of the dose, when symptoms resolve.
  - Escalate to full dose therapy as tolerated.

Direct Hyperbilirubinemia:

- If direct bilirubin is:
  - > 6 mg/dL (102.6 micromol/L): Omit the dose.
  - > 5 and ≤ 6 mg/dL (> 87.2 micromol/L and ≤ 102.6 micromol/L): Give 25% of the dose.
  - > 3.1 and ≤ 5 mg/dL (> 53 micromol/L and ≤ 85.5 micromol/L): Give 50% of the dose.
  - ≤ 3.1 mg/dL (53 micromol/L): Do not reduce the dose.
- Do not make up missed doses.

- Repeat direct bilirubin measurement within 48 hours before the next dose is due and calculate the dose based on this measurement.

Foot Drop, Paresis:

- < Grade 3: Do not reduce the dose.
- ≥ Grade 3: Dose modification is strongly discouraged.
  - If the investigator determines that dose modification is justified:
    - Give 50% of the dose.
    - Resume full dose therapy as soon as possible.
- Provide physical therapy at the investigator's discretion.

Hyponatremia/syndrome of inappropriate secretion of antidiuretic hormone (SIADH):

- Do not reduce the dose.

Jaw Pain:

- Do not reduce the dose.
- Provide analgesia at the investigator's discretion.

Severe Neuropathic Pain (≥ Grade 3):

- Dose modification is strongly discouraged.
- If the investigator determines that dose modification is justified:
  - Give 50% of the dose.
  - Resume full dose therapy as soon as possible.
- Provide analgesia at the investigator's discretion.

Vocal Cord Paralysis:

- Discontinue until symptoms subside.
- Resume at 50% of the dose.
- Escalate to full dose therapy as tolerated.

8.5 Concomitant Medications

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements.

All concomitant medications must be recorded on the subject's electronic case report form (eCRF) from signing of the ICF to 30 days following the last dose of study drug.

Blood products are not considered concomitant medications and must be recorded on the appropriate eCRF from signing of the ICF to 30 days following the last dose of study drug.

8.5.1 Required Concomitant Medications

All required and recommended concomitant medications are provided in Section 9, Supportive Care Requirements and Guidelines.

8.5.2 Excluded Concomitant Medications

- Marketed or investigational anticancer therapeutics that are not a component of this treatment regimen
- Radiotherapy
- Investigational agents for non-neoplastic conditions
- See Section 9.4 and Section 9.9.4, and Section 9.10 for instructions about azole antifungal agents and myeloid growth factors, respectively, as their administration is restricted to certain circumstances.

8.5.3 Drug-Drug Interactions

- Carfilzomib is primarily metabolized through peptidase and epoxide hydrolase activities.
  - Cytochrome P450 (CYP450)–mediated mechanisms play a minor role in the overall metabolism of carfilzomib. The PK profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers.
  - Carfilzomib is a P-glycoprotein (P-gp) substrate. The PK profile of carfilzomib is unlikely to be affected by P-gp inhibitors or inducers, given that carfilzomib is administered IV and is extensively metabolized.

8.6 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s), device(s), or combination product(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the Investigational Product Instruction Manual (IPIM).

9. Supportive Care Requirements and Guidelines

For sites outside of the US, equivalent medications for all agents listed in this section are acceptable. The sections below describe requirements for the phase 1 portion of this study; other therapies required for the phase 2 portion of the study are provided in Section 22.1.6.

9.1 Tumor Lysis Syndrome

Subjects at high risk of tumor lysis should be assessed rapidly for evidence of symptomatic hyperleukocytosis, TLS, and coagulopathy.

- Relevant laboratory tests from the screening period include:
  - Complete blood count (CBC)
  - Serum electrolytes, including calcium and phosphorus
  - Creatinine
  - Blood urea nitrogen (BUN)
  - Uric acid

Continued monitoring of these laboratory values at intervals suitable to the clinical condition is required, until abnormalities have resolved or the risk has abated. The risk for serious acute TLS usually subsides within the first 72 hours after initiation of therapy.

- If coagulopathy is suspected, monitoring of the following additional laboratory tests is strongly recommended:
  - Prothrombin and activated partial thromboplastin times
  - Fibrinogen
  - D-dimer
- To manage hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia, the following is required:
  - Begin allopurinol
    - Institutional guidelines for dosing and administration should be followed.
    - Continue until peripheral blasts and extramedullary disease have been reduced.
  - Treatment with Rasburicase should be considered for subjects with severe hyperuricemia, oliguria, or severe renal dysfunction.
    - Screening for glucose-6-phosphate dehydrogenase deficiency prior to Rasburicase administration is strongly recommended.
    - Institutional guidelines for dosing and administration should be followed.
  - Hydrate at least 100-125 mL/m²/h to maintain urine output > 3 mL/kg/h

  - Continue until peripheral blasts and extramedullary disease have been reduced.
  - Institutional guidelines for administration should be followed.
- If institutional practice includes alkalinization, alkalinize urine to maintain urine pH 6.5–7.5.
  - The regimen for alkalinizing urine is at the investigator's discretion.
  - Institutional guidelines for dosing and administration should be followed.
  - Alkalinization is not recommended when treating with Rasburicase.

9.2 Blood Products

- Blood products are provided at the discretion of the investigator.
- Institutional guidelines for administration should be followed.

9.3 Pneumocystis Prophylaxis

- Pneumocystis prophylaxis (PCP) must be provided throughout the study period.
- Oral administration of trimethoprim-sulfamethoxazole (TMP-SMX) is preferred, but alternative agents may be provided if there is a documented contraindication to TMP-SMX.
- Institutional guidelines for dosing and administration should be followed.
- For subjects with delayed recovery of peripheral blood counts investigators should consider replacing TMP-SMX after day 22 of induction with alternative therapy until recovery of bone marrow function, Atovoquone, aerosolized or IV pentamidine, dapsone, or other agent per institutional standards may be considered as short term alternative to TMP-SMX.

9.4 Fungal Prophylaxis

- Fungal prophylaxis must be provided during periods of neutropenia from the Induction Cycle through the end of study treatment.
- Echinocandin (ie, caspofungin or micafungin) or amphotericin agents are acceptable.
  - Institutional guidelines for dosing and administration should be followed.
  - Provide treatment level doses, rather than prophylactic doses.
- Azole antifungal agents (ie, fluconazole, itraconazole, voriconazole) given concurrently with vincristine may increase risk of neurotoxicity and their use as prophylaxis is not permitted.

9.5 Herpes Virus Prophylaxis

- Herpes simplex virus (HSV) prophylaxis must be provided throughout the study period for subjects with a history of documented or suspected HSV or varicella-zoster virus infection.
- Acyclovir or valacyclovir are acceptable.
- Institutional guidelines for dosing and administration should be followed.

9.6 Bacterial Prophylaxis

- Bacterial prophylaxis during periods of neutropenia is strongly recommended, due to the high risk for serious bacterial infections in this population.
- Institutional guidelines for dosing and administration should be followed.

9.7 Intravenous Immunoglobulin Supplementation

- Intravenous immunoglobulin (IVIg) supplementation for subjects with hypogammaglobulinemia ($<$ 500 mg/dL) is recommended, due to the high risk for infections in this population. IV Ig infusions should use concentrations no greater than 5 g/dL to avoid renal toxicity.
- Institutional guidelines for dosing and administration should be followed.

9.8 Central Line Care

- Measures to minimize the risk for catheter-associated serious bacterial infections must be taken throughout the study period.
- The specific regimen for central line care should be consistent with institutional guidelines.

9.9 Fever and Neutropenia

9.9.1 Definition

- Fever and neutropenia is defined as a temperature $\geq$ 38.5°C on a single occasion, or $>$ 38°C on 2 occasions within 2 hours, and an ANC $<$ 0.50 x 10^9/L.

9.9.2 Evaluation

- Blood cultures should be obtained from all lumens.
- Additional cultures (urine, cerebral spinal fluid [CSF], respiratory, etc.) are obtained at the investigator's discretion and should be based on the specific clinical presentation.
- Chest radiographs and other imaging studies are obtained at the investigator's discretion and should be based on the specific clinical presentation.

9.9.3 Treatment

- Broad spectrum coverage for both gram-negative and gram-positive infection must be provided IV as soon as possible.
- Additional gram-negative coverage and glycopeptide agents are at the investigator's discretion and should be based on the specific clinical presentation.
- Antifungal, antiviral, and other additional agents are at the investigator's discretion and should be based on the specific clinical presentation.
- Institutional guidelines for dosing and administration should be followed.

9.9.4 Persistent or Recurrent Symptoms

- If fever persists for $>$ 96 hours or recurs after 3 days of treatment, surveillance for fungal infections or other occult infections is strongly recommended.
  - Studies to consider include, but are not limited to:

  - Computed tomography (chest, sinuses, abdomen, etc.)
  - Bronchoalveolar lavage
  - Viral PCR (adenovirus, Epstein-Barr virus, cytomegalovirus, etc)

- If not already part of the treatment regimen, treatment dose antifungal therapy should be initiated.
  - Although prohibited for prophylaxis, azoles may be provided at the investigator's discretion.
  - Institutional guidelines for dosing and administration should be followed.
- The addition of other antimicrobial agents should be seriously considered and is at the investigator's discretion.
  - Institutional guidelines for dosing and administration should be followed.

9.10 Myeloid Growth Factors

- Granulocyte colony stimulating factors may be administered starting 24 hours after the last dose of cytotoxic chemotherapy per investigators discretion and are recommended for subjects that are likely to have delayed neutrophil recovery, such as multiply relapsed, a history of prior stem cell transplant, or a history of delayed neutrophil recovery after cytotoxic chemotherapy. Institutional guidelines for dosing and administration should be followed.
- Administration of myeloid growth factors in response to severe infection or fever and neutropenia is at the investigator's discretion

9.11 Gastritis Prophylaxis

- Prophylaxis with either a histamine 2 (H2) blocker or proton pump inhibitor is required during the Induction Cycle.
- Continued administration of gastritis prophylaxis during the optional cycle of consolidation therapy is at the investigator's discretion.

9.12 Prevention and Management of Nausea and Vomiting

- Prophylactic antiemetic administration is strongly recommended when emetogenic chemotherapy, including IT therapy, is administered.
- The precise antiemetic regimen is at the investigator's discretion.
- Corticosteroid administration as part of the antiemetic regimen is prohibited.
- Institutional guidelines for dosing and administration should be followed.
- Intravenous fluids and/or nutrition support should be provided, if nausea or vomiting prevent adequate intake of fluids or nutrients.

9.13 Constipation Prophylaxis

- Administration of stool softeners and/or laxatives to prevent constipation is strongly recommended.
- The precise bowel regimen is at the investigator's discretion.
- Institutional guidelines for dosing and administration should be followed.

9.14 Contraception

The phase 2 protocol, including the contraception requirements for the phase 2 is provided in Appendix K.

9.14.1 Female of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered of child bearing potential:

1. Premenopausal female with 1 of the following:
   a. Documented hysterectomy
   b. Documented bilateral salpingectomy
   c. Documented bilateral oophorectomy

   Note: Site personnel documentation from the following sources is acceptable: 1) review of subject medical records, 2) subject medical examination, or 3) subject medical history interview.
2. Premenarchal female
3. Postmenopausal female
   a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b. Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

9.14.2 Female Subjects

Female subjects of childbearing potential must agree to use one highly effective method of contraception (as described in the table below) during treatment and for an additional 12 months after the last dose of protocol-required therapies. Contraception must be in place at least 2 weeks prior to the first study treatment.

Highly Effective Contraceptive Methods for Female Subjects *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal) • Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) • Intrauterine device (IUD) • Intrauterine hormonal-releasing system (IUS) • Bilateral tubal ligation/occlusion • Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success) • Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence must be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)

If a female subject is suspected of being pregnant, the protocol-required therapies must be stopped immediately and may not be resumed until absence of pregnancy has been medically confirmed.

9.14.3 Male Subjects

If the male's sole sexual partner is of non-childbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study. The definition of non-childbearing potential is provided above.

Male subjects with a partner of childbearing potential must agree to not father a child during treatment and for an additional 12 months after the last dose of protocol-required therapies.

Contraceptive options for male subjects include:

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies). The reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject. or
- Use a condom during treatment and for an additional 12 months after the last dose of protocol-required therapies.

The female partner is to use an acceptable method of effective contraception such as: hormonal, IUD, IUS, female barrier method (diaphragm, cervical cap, contraceptive sponge [a female condom is not an option because there is a risk of tearing when both

partners use a condom]). Male subjects must not donate sperm during treatment and for an additional 12 months after the last dose of protocol-required therapies.

Male subjects with a pregnant partner must practice sexual abstinence or wear a condom to prevent exposure of the unborn child to study drugs through semen.

9.14.4 Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical trials include: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to fetus if they become pregnant or father a child during treatment and for 6 months after the last dose of protocol-required therapies.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception for an increased length of time. In addition, male subjects may also be required to alter the duration and methods of contraception. The investigator must discuss these topics with subjects.

10. Study Procedures

The phase 2 protocol, including phase 2 part of the study procedures, is provided in Appendix K.

10.1 On-study Assessments

All required and optional procedures to take place during the Lead-in Window, Induction Cycle, and Optional Consolidation Cycle are provided in the following sections and, where needed, are further described in the text that follows. Single-page assessment guides are provided in Appendix B, Appendix C, and Appendix D.

10.1.1 Lead-in Window (Dose Escalation 1 [R3] Only)

Refer to Section 8.1.1, Table 4, for treatment and response assessment details during the Lead-in Window.

Table 9. Phase 1 On-study Assessments: Lead-in Window

Assessment	Cycle Day		
	1	2	8
Physical examination	X		X
Lumbar puncture			
CNS-negative	X[a]		X
CNS-positive	X[a]		X
Local laboratory evaluations			
CBC with differential and platelet count	X[a]		X
Electrolytes: Na, K, Cl, CO_2, Ca, Mg, P	X[a]		X
Blood glucose	X[a]		X
Renal function: BUN, Cr	X[a]		X
Hepatic function: AST, ALT, total and direct bilirubin, ALP, albumin	X[a]		X
Pancreatic function: amylase, lipase	X[a]		X
Uric acid	X[a]		X
Bone-specific ALP	X		
Correlative study measurements			
Pharmacokinetic studies	X		
[redacted]	[redacted]	[redacted]	
[redacted])	[redacted]		[redacted]
Response assessment/bone marrow aspirate (including MRD)			X

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CNS = central nervous system; Cr = serum creatinine; ECG = electrocardiogram; MRD = minimal residual disease; NM-GFR = nuclear magnetic-glomerular filtration rate; ULN = upper limit of normal.

[a] Assessments from the screening period must have been obtained within 72 hours before enrollment (or for lumbar puncture, within 7 days before enrollment) and no repeat Day 1 study assessments are required, except for repeat assessments of the blood when the initiation of study treatment occurs > 48 hours after these labs were obtained or at the discretion of the investigator.

[redacted]

10.1.2 Induction (Dose Escalation 1 [R3] and Dose Escalation 2 [VXLD])

Refer to Section 8.1.2, Table 5, for treatment and response assessment details during the Induction Cycle.

Table 10. Phase 1 On-study Assessments: Induction Cycle (Dose Escalation 1 [R3] and Dose Escalation 2 [VXLD])

Assessment	Cycle Day							
	1	2	8	15	22	29	35	42
Physical examination	X[a]		X	X	X	X		
Lumbar puncture (CNS-negative)								
Dose Escalation 1 (R3)	X							
Dose Escalation 2 (VXLD)	X[a]		X					
Lumbar puncture (CNS-positive)								
Dose Escalation 1 (R3)	X		X	X		X		
Dose Escalation 2 (VXLD)	X[a]		X	X	X	X		
Local laboratory evaluations								
CBC with differential and platelet count	X[a]		X	X	X	X	X[d]	X[d]
Electrolytes: Na, K, Cl, CO_2, Ca, Mg, P	X[a]		X	X	X	X		
Blood glucose	X[a]		X	X	X	X		
Renal function: BUN, Cr	X[a]		X	X	X	X		
Hepatic function: AST, ALT, total and direct bilirubin, ALP, albumin	X[a]		X	X	X	X		X[d]
Pancreatic function: amylase, lipase	X[a]		X	X	X	X		
Uric acid	X[a]		X	X	X	X		
Bone-specific ALP	X[b]					X		
Correlative study measurements								
Pharmacokinetic studies			X					
[redacted]	[redacted]	[redacted]				[redacted]		
[redacted]	[redacted]					[redacted]		
Response assessment/bone marrow aspirate (including MRD)						X		

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CNS = central nervous system; Cr = serum creatinine; MRD = minimal residual disease

[a] For subjects in the Dose Escalation 2 (VXLD) portion of the study, assessments from the screening period must have been obtained within 72 hours before enrollment (or for lumbar puncture, within 7 days before enrollment) and no repeat Day 1 study assessments are required, except for repeat assessments of the blood when the initiation of study treatment occurs > 48 hours after these labs

[redacted]

[d] Laboratory assessments after day 29 of induction should be collected up to start of consolidation.

10.1.3 Optional Consolidation

Refer to Section 8.1.3, Table 7, for treatment and response assessment details during the Optional Consolidation Cycle.

Table 11. Phase 1 On-study Assessments: Optional Consolidation Cycle

Assessment	Cycle Day					
	1	2	8	15	22	29
Physical examination	X		X	X	X	X
Lumbar puncture						
CNS-negative	X		X	X	X	
CNS-positive	X		X	X	X	X[a]
Local laboratory evaluations						
CBC with differential and platelet count	X		X	X	X	X
Electrolytes: Na, K, Cl, CO_2, Ca, Mg, P	X		X	X	X	X
Blood glucose	X		X	X	X	X
Renal function: BUN, Cr	X		X	X	X	X
Hepatic function: AST, ALT, total and direct bilirubin, ALP, albumin	X		X	X	X	X
Pancreatic function: amylase, lipase	X		X	X	X	X
Response assessment/bone marrow aspirate (including MRD)						X

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CNS = central nervous system; Cr = serum creatinine; MRD = minimal residual disease

[a] Required only for subjects who remain CNS-positive on Day 22.

10.1.4 Additional Procedure Details

Physical Examination

During study treatment, a physical examination must include all of the following and be completed prior to the delivery of study treatment on the days indicated in Table 9, Table 10, and Table 11:

- Updated documentation of all current medications
- Vital Signs
  - Temperature: The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs case report form (CRF).
  - Heart Rate
  - Respiratory Rate
  - Systolic and Diastolic Blood Pressures: Subject should be in a rested and calm state for at least 5 minutes before blood pressure measurements are conducted. The position selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF.

- Weight
- Height and BSA (only required prior to beginning the Optional Consolidation Cycle; see Section 8.1.3)
- Examination of all of the following:
  - Head
  - Ears
  - Eyes
  - Nose
  - Oropharynx
  - Heart
  - Lungs
  - Abdomen
  - Extremities
  - Lymph Nodes
  - Skin
  - Nervous System
- Determination of the updated NCI-CTCAE (Version 4.03) grade for all abnormal physical examination findings.
  - Clinically significant abnormal findings that are new or represent a worsening after the signature of the ICF must be reported as adverse events.

Laboratory Evaluations

Laboratory evaluations of the blood must be obtained and results reviewed prior to the delivery of study treatment on the days indicated in Table 9, Table 10, and Table 11 but may be obtained as early as 48 hours in advance.

The first blood sample for bone-specific ALP must be collected prior to the initiation of study treatment; however, results are not required for study treatment to begin.

All hepatitis testing will be performed locally. All subjects will be tested at screening for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc), unless performed within 6 months of screening and there was no change in the subject's risk factors within these 6 months (Table 1). Subjects with positive testing or a history of prior HBV infection should have consultation with a specialist and must have HBV-DNA testing at screening and again at safety follow up. Subjects that have received Hepatitis B vaccination with only anti--HBs positivity and no clinical signs of hepatitis do not require HBV-DNA monitoring.

Pharmacokinetic Studies

Blood samples will be collected from all subjects for determination of plasma concentrations of carfilzomib on Day 1 of the Lead-in Window (Dose Escalation 1 only) and Day 8 of the Induction Cycle (Dose Escalation 1 [R3] and Dose Escalation 2 [VXLD]) at the following time points:

- Predose
- 15 minutes after the start of infusion
- Immediately (within 2 minutes before the end of infusion)
- 10 minutes, 30 minutes, and 1, 2, and 4 hours after the end of the infusion

[redacted]

[redacted]

10.2 Response Assessment

The Lead-in Window Day 8 (for Dose Escalation 1 [R3]), the Induction Cycle Day 29 (for Dose Escalation 1 [R3] and Dose Escalation 2 [VXLD]), and the Optional Consolidation Cycle Day 29 (when applicable) response assessments will be performed by the investigator. Bone marrow aspiration, lumbar puncture, physical examination (including testicular examination), and CBC with differential and platelets will be performed to assess the disease status. Lumbar puncture to assess disease status will not be required after the second lumbar puncture for subjects who are CNS-negative. Subjects who are CNS-positive must have 2 consecutive lumbar punctures without evidence of leukemia, before lumbar puncture is no longer required for assessment of disease status.

A portion of the bone marrow collected at the time of these response assessments will be submitted to a central laboratory, for determination of MRD. Instructions for collection and submission are provided in the Laboratory Manual.

The criteria for determining treatment response are defined in the sections that follow. See Appendix K for response definitions for phase 2.

10.2.1 Complete Remission

Complete remission (CR) is defined as the attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease and with recovery of peripheral counts (ANC $>$ 750 mcl and platelet count $>$ 75,000 mcl). Qualifying marrow and peripheral counts should be performed within 1 week of each other.

10.2.2 Complete Remission Without Platelet Recovery

Complete remission without platelet recovery (CRp) is defined as the attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease and with recovery of ANCs (ANC $>$ 750 mcl), but with insufficient recovery of platelets ($<$ 75,000 mcl).

10.2.3 Complete Remission With Incomplete Hematologic Recovery

Complete remission with incomplete hematologic recovery (CRi) is defined as the attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease and with no recovery of ANCs (ANC < 750/mcl), with or without insufficient recovery of platelets (< 75,000/mcl).

10.2.4 Partial Response

Partial response (PR) is defined as the complete disappearance of circulating blasts and achievement of M2 bone marrow status, without new sites of extramedullary disease, and with recovery of ANCs (ANC > 750 mcl).

10.2.5 Stable Disease

Stable disease is defined as the subject not satisfying the criterion for progressive disease (PD), or has recovery of ANC > 750 mcl and fails to qualify for CR, CRp, or PR.

10.2.6 Progressive Disease

Progressive Disease is defined as an increase of at least 25% in the absolute number of circulating leukemic cells or bone marrow blasts, development of new sites of extramedullary disease, or other laboratory or clinical evidence of PD, with or without recovery of ANC or platelets.

10.2.7 Induction Death

An induction death (ID) is defined as any death that occurs during the Lead-in Window or as any death that occurs up to Day 42 of the Induction Cycle, provided that subsequent therapy has not been administered and the death occurred prior to response evaluation, or the death occurred after response evaluation but prior to subsequent therapy in a subject that did not demonstrate persistent leukemia (stable or progressive disease).

10.2.8 Not Evaluable

A subject considered to be not evaluable (NE) is one who does not satisfy the criteria for PD or ID, having had no marrow evaluation or inadequate marrow cell count.

11. Study Discontinuation

The phase 2 protocol, including details on study discontinuation in phase 2, is provided in Appendix K.

11.1 Withdrawal of Subjects From Treatment

Subjects may withdraw from study treatment at any time.

Subjects are considered to have reached the planned end of study treatment when the Induction or Optional Consolidation Cycles are completed. The investigator must remove a subject from study treatment prior to the planned end of treatment for the following reasons:

- Unacceptable toxicity
- Subject or their legally acceptable representative withdraws consent for study treatment
- Requirement for alternative therapy
- Noncompliance with study procedures, including administration of prohibited medications
- Pregnancy

With the exception of those who withdraw consent for further follow-up, all subjects must be followed for 30 days after their final dose of study treatment or until all carfilzomib-related toxicity has resolved or stabilized, whichever is longer.

Subjects determined to be not evaluable may be replaced. Decisions regarding subject replacement will be made by the Sponsor and will be based on the need for additional subjects to do 1 or more of the following:

- Determine the MTD.
- Ensure a minimum of 3 subjects in a particular age group.

11.2 End-of-study Assessments

The End-of-Study Assessments must be completed 30 days (± 4 days) following the last dose of study treatment. For subjects who complete the End-of-Study Assessment less than 30 ± 4 days following the last dose of study treatment, a follow-up of ongoing AEs should be attempted by telephone and documented in the subject's source file. All AEs must be followed until resolution, unless the investigator has determined that the event has stabilized or is not expected to improve. The End-of-Study Assessments are presented in Table 12 and described in the text below.

Table 12. Phase 1 End-of-study Assessments

Assessment	30 Days (± 4 Days) After Last Dose of Study Treatment
Physical examination	X
Local laboratory evaluations	X
CBC with differential and platelet count	X
Electrolytes: Na, K, Cl, CO_2, Ca, Mg, P	X
Blood glucose	X
Renal function: BUN, Cr	X
Hepatic function: AST, ALT, total and direct bilirubin, ALP, albumin	X
Hepatitis B testing	X[a]
Pancreatic function: amylase, lipase	X

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; Cr = serum creatinine; HBV = hepatitis B virus
[a] Only in subjects with positive hepatitis B serology at screening or past history of HBV infection.

Physical Examination

A complete history and physical examination must include all of the following:

- Review of medical and surgical histories, including:
  - Documentation of all current medications
- Vital Signs:
  - Temperature
  - Heart Rate
  - Respiratory Rate
  - Systolic and Diastolic Blood Pressures
- Weight, Height, and BSA
- Performance Status Assessment (Appendix F):
  - Lansky score if < 16 years of age
  - Karnofsky score if ≥ 16 years of age
- Examination of all of the following:
  - Head
  - Ears
  - Eyes
  - Nose
  - Oropharynx
  - Neck
  - Heart
  - Lungs
  - Abdomen

  - Genitalia
  - Back
  - Extremities
  - Lymph Nodes
  - Skin
  - Nervous System
- Determination of the updated NCI-CTCAE (Version 4.03) grade for all abnormal physical examination findings.

11.3 Study Termination

The Sponsor has the right to terminate this study or a study site from participating in a study at any time.

Reasons for terminating the study overall or at a specific study site may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other carfilzomib studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- Investigator does not adhere to the protocol or applicable regulatory requirements in conducting the study
- The Data Monitoring Committee (DMC) recommends termination of the study

12. Adverse Events and Serious Adverse Events (SAES)

The phase 2 protocol, including details regarding adverse events and serious adverse events, is provided in Appendix K. .

12.1 Adverse Event Reporting

12.1.1 Definitions

An AE is any untoward medical occurrence in a study subject administered an investigational product(s) regardless of the causal relationship with treatment. For the purposes of this study, an AE is defined as any untoward medical occurrence that takes place following the signing of the ICF.

An AE, therefore, can be any unfavorable and unintended sign (including laboratory finding), symptom or disease temporally associated with participation in an investigational study, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the subject or the subject's legally acceptable representative signs the ICF for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

All reported AEs will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). The NCI-CTCAE version 4.03 will be used to describe the event and to assess the severity of AEs. For AEs not adequately addressed in the NCI-CTCAE Version 4.03 (Table 13) will be used.

Table 13. Toxicity Grading for Adverse Events not Covered in the NCI-CTCAE (Version 4.03)

Severity	Description
GRADE 1 - Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
GRADE 2 – Moderate	Minimal, local, or noninvasive intervention indicated, limiting age-appropriate instrumental ADL
GRADE 3 – Severe	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
GRADE 4 – Life-threatening	Life-threatening consequences; urgent intervention indicated
GRADE 5 – Fatal	Death

ADL = activities of daily living

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the current IB as an adverse drug reaction or is not listed at the specificity or severity that has been observed. AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with a particular study drug are considered “unexpected.” For example, an event more specific or more severe than described in the IB would be considered “unexpected.” Any condition, laboratory abnormality, or physical finding with an onset date prior to the subject or their legally acceptable representative signing the ICF is considered to be pre-existing in nature and part of the subject’s medical history.

12.2 Causality

A suspected adverse event means any AE for which there is reasonable possibility that the study drug caused the AE. “Reasonable possibility” means that there is evidence to suggest a causal relationship between the drug and the AE.

The relationship of the AE to the study drug should be assessed using the following criteria:

YES; the event is suspected to be related if:

- There is a clinically plausible time sequence between the AE onset and administration of study treatment; and/or
- There is a biologically plausible mechanism for the study treatment to cause or contribute to the AE; and/or
- The event responds to withdrawal of the study medication (de-challenge) and/or recurs or worsens with re-challenge (when clinically feasible); and/or
- The AE cannot be reasonably attributed to concurrent or underlying illness, other drugs, or procedures

NO; the event is not suspected to be related if:

- The AE is more likely to be explained by the subject's clinical state, underlying disease, concomitant medical, study or non-study procedure; and/or
- The time occurrence of the AE is not reasonably related to administration of study treatment; and/or
- The event is not related to the investigational product(s)

In the event of a possible drug-related AE, the investigator should, to the best of his/her ability, assess its relationship to each of the study drugs: carfilzomib, dexamethasone, mitoxantrone, PEG-asparaginase, vincristine, 6-mercaptopurine, cyclophosphamide, cytarabine, or IT hydrocortisone, cytarabine, or methotrexate.

12.3 Adverse Events Reporting Procedures

12.3.1 General

All AEs (eg, any new event or worsening in severity or frequency of a pre-existing condition or laboratory finding) with an onset date after the subject or their legally acceptable representative signs the informed consent for participation in the clinical trial through 30 days after any study drug in the combination was received must be promptly documented on the AE eCRF via the electronic data capture (EDC) system. AEs that are laboratory findings that do not result in a clinical action or alter treatment do not require reporting as AEs, unless the investigator considers the laboratory finding to be clinically significant. Details of the event must include severity, relationship to study drug(s), duration, action taken, and outcome. Whenever possible, reporting specific diagnosis is preferred when reporting AEs in the AE eCRF rather than reporting individual signs and symptoms. Serious adverse events will be recorded on the AE eCRF and on the SAE reporting form (see Section 12.5, Serious Adverse Event Reporting and Documentation Requirements). In addition, the investigator should report any AEs that may occur after this time period which are assessed to have a reasonable possibility of being associated with study drug. If the subject is enrolled but discontinues

participation in the study prior to receiving study drug, AEs must be reported through the End-of-Study Assessment.

If initiation of new anticancer therapy occurs within 30 days following the last dose of study drug(s), the date of new anticancer therapy will be recorded on the appropriate eCRF.

All AE severity changes must be recorded on the AE CRF as separate events. Every AE severity grade change must be recorded on the AE CRF. All AEs that are considered related to study drug and all SAEs regardless of relationship to study drug must be followed to resolution or stabilization if improvement is not expected. AEs which completely resolve and then recur should be recorded as a new AE. For subjects who complete the End-of-Study Assessment less than 30 days following the last dose of study drug, a follow-up of ongoing AEs should be attempted by telephone and documented in the subject's source file. AEs continuing at 30 days after the last dose of study treatment should have a comment in the source file by the investigator that the event has stabilized or is not expected to improve.

The investigator is responsible for evaluating all AEs, obtaining supporting source documents, and determining that documentation of the event is adequate.
The investigator may delegate these duties to sub-investigators and must ensure that these sub-investigators are qualified to perform these duties under the supervision of the investigator and that they are listed on the FDA Form 1572.

12.3.2 Disease Progression

Disease progression will be documented in an eCRF intended to capture PD information. Signs and symptoms related to disease progression should be reported in the appropriate case report form (CRF) as an AE or as an SAE (if the event in question meets the criteria for seriousness). Verbatim terms such as "disease progression," "progressive disease," etc. should not be reported as AEs or SAEs unless the investigator considers the progression to be atypical, accelerated, or caused by the study drug. Similarly, deaths occurring as a result of disease progression should be reported on the eCRF intended to capture death information and should not be reported as SAEs.

12.4 Serious Adverse Event Definitions

An SAE is an AE that meets 1 or more of the following criteria:

- Death
- Life-threatening experience defined as any adverse experience that places the subject, in the view of the sponsor or investigator, at immediate risk of death at the time of occurrence; ie, it does not include a reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of an existing hospitalization (except scheduled hospitalizations for a nonacute, unrelated cause such as elective surgery)
- Results in persistent or significant disability/incapacity (ie, substantial disruption in a subject's ability to conduct normal activities of daily living)
- Is a congenital anomaly/ birth defect in the offspring of an exposed female subject or offspring of a female partner of a male subject

Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered SAEs when, based on appropriate medical judgment, they jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

12.5 Serious Adverse Event Reporting and Documentation Requirements

Amgen Global Patient Safety must be notified of the occurrence of any SAE within 24 hours of the investigator, designee, or site personnel's knowledge of the event. The SAE will be reported by completing and submitting the SAE report form through the EDC system. In the event that the EDC system is not available, paper SAE report forms may be used to report the SAE to Amgen Global Patient Safety (Appendix H). Please refer to the SAE Reporting Guidelines in the study reference manual.

Follow-up reports must be submitted in a timely fashion as additional information becomes available.

The investigator is responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committees (IEC) in accordance with local regulations, of all SAEs. The sponsor may request for additional source documentation pertaining to the SAE from the investigational site. If a subject is permanently withdrawn from the study due to an SAE, this information must be included in the initial or follow-up SAE report in the eCRF.

The sponsor is responsible for notifying the appropriate global health authorities of SAEs, when required, and in accordance with applicable laws and regulations.

All SAEs occurring from the time that the subject signs consent for study participation and through 30 days after the last administered dose of study drug will be reported on the AE eCRF, regardless of whether new chemotherapy regimens are initiated. (Additional information is provided in Section 12.3.1). All SAEs, regardless of relationship to study drug, must be followed to resolution or to stabilization if improvement or resolution is not expected.

12.6 Pregnancy and Lactation Reporting

If a female subject becomes pregnant or a male subject fathers a child while the subject is taking protocol-required therapies, report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur 6 months after the last dose of protocol-required therapies.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix I). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

If a female breastfeeds while taking protocol-required therapies, report the lactation case to Amgen as specified below.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix J). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

If the subject becomes pregnant while taking an Amgen drug, the study drugs will be immediately discontinued. The investigator will discuss the risks and concerns of investigational drug exposure to a developing fetus and counsel the subject and/or pregnant partner (or ensure that such counseling is provided).

Newborns should be followed for a minimum of 12 weeks.

13. Statistics

The phase 2 protocol, including the statistical considerations for phase 2, is provided in Appendix K.

13.1 Study Endpoints

13.1.1 Primary Endpoints

The primary endpoints for this study are:

- Safety and tolerability of carfilzomib alone and in combination with induction chemotherapy as defined by the type, incidence, severity, and outcome of AEs; changes from baseline in key laboratory analytes, vital signs, and physical findings. Time to toxicity will be evaluated to differentiate single-agent carfilzomib from carfilzomib in combination with induction chemotherapy
- Determination of the MTD as the dose that has the highest posterior probability of having a DLT rate within the target toxicity interval (20%–33%), while the posterior probability of excessive/unacceptable toxicity (> 33%–100%) is less than 40% (per BLRM algorithm), or the stopping rules as specified in Section 5.2, and per CSRC recommendation.

13.1.2 Secondary Endpoints

The secondary endpoints for this study are:

- Pharmacokinetic parameters, principally maximum plasma concentration (C_{max}) and area under the curve (AUC), alone and in combination with induction chemotherapy, derived from levels of carfilzomib assayed in PK samples
- Combined proportion of subjects who achieve CR or CRp at the end of the Induction Cycle
- Proportion of subjects who achieve MRD status $< 10^{-3}$ and $< 10^{-4}$ lymphoblasts at the end of the Induction Cycle as assessed by next generation sequencing (NGS)

13.2 Analysis of the Conduct of the Study

Subject enrollment, treatment, duration of follow-up, and discontinuation from the study (including reasons for discontinuation) will be summarized by dose levels.

13.3 Independent Review Committee

There will not be an Independent Review Committee for this study.

13.4 Cohort Safety Review Committee

The Cohort Safety Review Committee (CSRC) activities were governed by a separate charter (on file) for the R3 dose escalation and first 4 cohorts of the VXLD dose escalation. This section replaces the prior charter and governs the activities of the CSRC for all remaining cohorts of the VXLD dose escalation.

The primary objective of the study is to determine the MTD of carfilzomib in combination with standard of care backbone chemotherapy (VXLD). The CSRC is a cross-functional team whose purpose is to ensure the safety of subjects being treated with carfilzomib in combination with VXLD by reviewing safety data and DLTs after each cohort has completed the induction cycle, and to make recommendations on the next dose level to be evaluated based on that review and the recommendations of the Bayesian logistic regression model.

The voting members of the CSRC include the 2 lead investigators (1 representative from each consortium partnering on the study), the Amgen medical monitor, and the Amgen

global safety officer. Additional required non-voting members include the Amgen clinical trial manager and biostatistician. Optional attendees may include, but are not limited to the clinical program manager(s) and the investigators (or their designees) for the subjects under review. If a lead investigator is not available, the Amgen medical monitor will contact them and provide a summary of the meeting. The absent member will be allowed to vote post-meeting.

The CSRC will meet after each cohort of 3 DLT evaluable subjects have completed the induction and DLT evaluation periods. The Bayesian logistic regression model will be updated, and the NCRM will recommend the next dose level from the updated probabilities for the target toxicity interval and the excessive-unacceptable toxicity interval. The DLT evaluation period starts with the first dose of planned induction therapy (whether carfilzomib or backbone chemotherapy) and continues for at least 29 days and up to 45 days from the first dose of therapy. The conditions ending the DLT evaluable period are identified in Section 8.3. A CSRC meeting may be called by the Amgen medical monitor after 2 subjects have been enrolled if a safety concern is identified. Subjects who discontinue treatment, receive a dose modification, or miss doses of carfilzomib because of a non-dose-limiting toxicity adverse event or deviation from the protocol will be replaced, but their safety information will be considered in the CSRC's decisions.

All available study data, including data collected after the DLT evaluable period, and including eligibility, demographics, investigational product administration, medical and surgical history, prior leukemia therapy, concomitant medications, adverse events, vital signs, laboratory data, and available PK data will be reviewed. The database will not be cleaned, an as-is snapshot of the database will be used in the analysis. In addition to DLTs, all $\geq$ grade 3 toxicities not meeting DLT criteria and serious adverse events (of all grades) will be reviewed and may be considered along with the dose level recommended by the Bayesian logistic regression model in CSRC decisions.

The following decisions may be made by the CSRC:

- Increase the dose level by 1 step or decrease the dose level by 1 or more steps
- Note: No dose level skipping will be allowed in dose escalation decisions. There is no constraint on de-escalation decisions.
- Expand the current dose level by 3 subjects
- Halt enrollment, recommend the MTD based on available data, and recommend the dose for phase 2 if the Bayesian algorithm stopped because of the stopping

rules listed in Section 5.2 or because a safety signal is identified that in the opinion of the CSRC warrants stopping the trial

If the CSRC decision results in a tie vote, the available study data will be provided to the Amgen Hematology/Oncology Therapeutic Area head for final determination.

All other operational aspects of the CSRC meetings will follow Amgen processes for Dose Level Review Meetings.

The CSRC activities will stop after the end of the phase 1 part of the study.

13.5 Data Monitoring Committee

An independent DMC will be convened for this study and will act in an advisory capacity to the sponsor with respect to safeguarding the interests of study subjects, assessing interim safety and efficacy data, and monitoring the overall conduct of the study. The database will not be cleaned, an as-is snapshot of the database will be used in this analysis. To enhance the integrity of the study, the DMC may also formulate recommendations relating to the eligibility, recruitment, and retention of subjects, their management, improving adherence to protocol treatment, and the procedures for data management and quality control.

The details of the DMC, including the roles and responsibilities of the involved parties, will be described in the DMC Charter. The DMC will meet to review safety data no less frequently than every 6 months. Unplanned safety review meetings of the DMC may be called at any time if earlier review of safety data is warranted.

Details of the DMC for the phase 2 portion of the study are provided in Section 27.

13.6 Statistical Methods

Descriptive statistics will be used to summarize enrollment, subject demographic and baseline characteristics, and discontinuation from the study. Eligibility exceptions and important protocol deviations will be summarized.

Data from Dose Escalation 1 (R3) and Dose Escalation 2 (VXLD) will be analyzed separately.

Amgen will set a final analysis data cut-off date for safety, efficacy, and other analyses in anticipation of the date when all subjects have completed the study. At that time the database will be cleaned, processed and a locked database will be used in the analysis. The final analysis will address all the study objectives.

13.6.1 Efficacy Analyses

The primary efficacy analysis will be based on subject data collected through study discontinuation or at the end of maximal treatment duration plus 30 days of safety follow-up, whichever occurs first. Primary analyses will be based on the Safety Evaluable Population, defined as subjects receiving treatment with any amount of the study treatment regimen (chemotherapy backbone, carfilzomib, and any IT chemotherapy drugs). Additional efficacy analyses will be performed using the Efficacy Evaluable Population, defined as subjects who are included in the safety evaluable population, and have a baseline disease assessment and at least 1 postbaseline disease assessment, or dropped out due to AE prior to the postbaseline disease assessment.

All summaries will be presented by the overall Safety Population and by the assigned dose level. Response assessment data including the status of CR/CRp and the proportion of subjects who achieve MRD status $< 10^{-3}$ and $< 10^{-4}$ lymphoblasts will be listed.

13.6.2 Safety Analysis

The safety analyses will be based on the safety evaluable population, which is defined as all subjects who receive any amount of the study treatment regimen (chemotherapy backbone, carfilzomib, and any IT chemotherapy drugs).

Safety and tolerability will be assessed through summaries of study drug administration, DLTs, AEs, changes in selected laboratory analytes, vital signs, and physical findings by dose level, and for all subjects.

The number of DLTs and AEs at each dose level will be summarized separately for the carfilzomib single-agent Lead-in Window and the Induction Cycle. Adverse events will also be summarized separately for subjects who receive the optional cycle of consolidation chemotherapy.

Means and standard deviations will be used to summarize the total dose for each component of study drug received. All summaries will be presented by the assigned dose level and for all subjects.

All AE data will be listed by study site, dose level, subject identification number, and study day. All AEs will be summarized by preferred term and NCI-CTCAE (Version 4.03) toxicity grade. In addition, all SAEs, including deaths, will be listed separately and summarized.

Relevant laboratory and vital sign (temperature, heart rate, respiratory rate, and blood pressure) data will be displayed by visit and time (when available), with NCI-CTCAE (Version 4.03) Grade 3 and 4 values identified where appropriate. Additionally, all laboratory data will be summarized by NCI-CTCAE grade.

13.6.3 Correlative Study Analyses

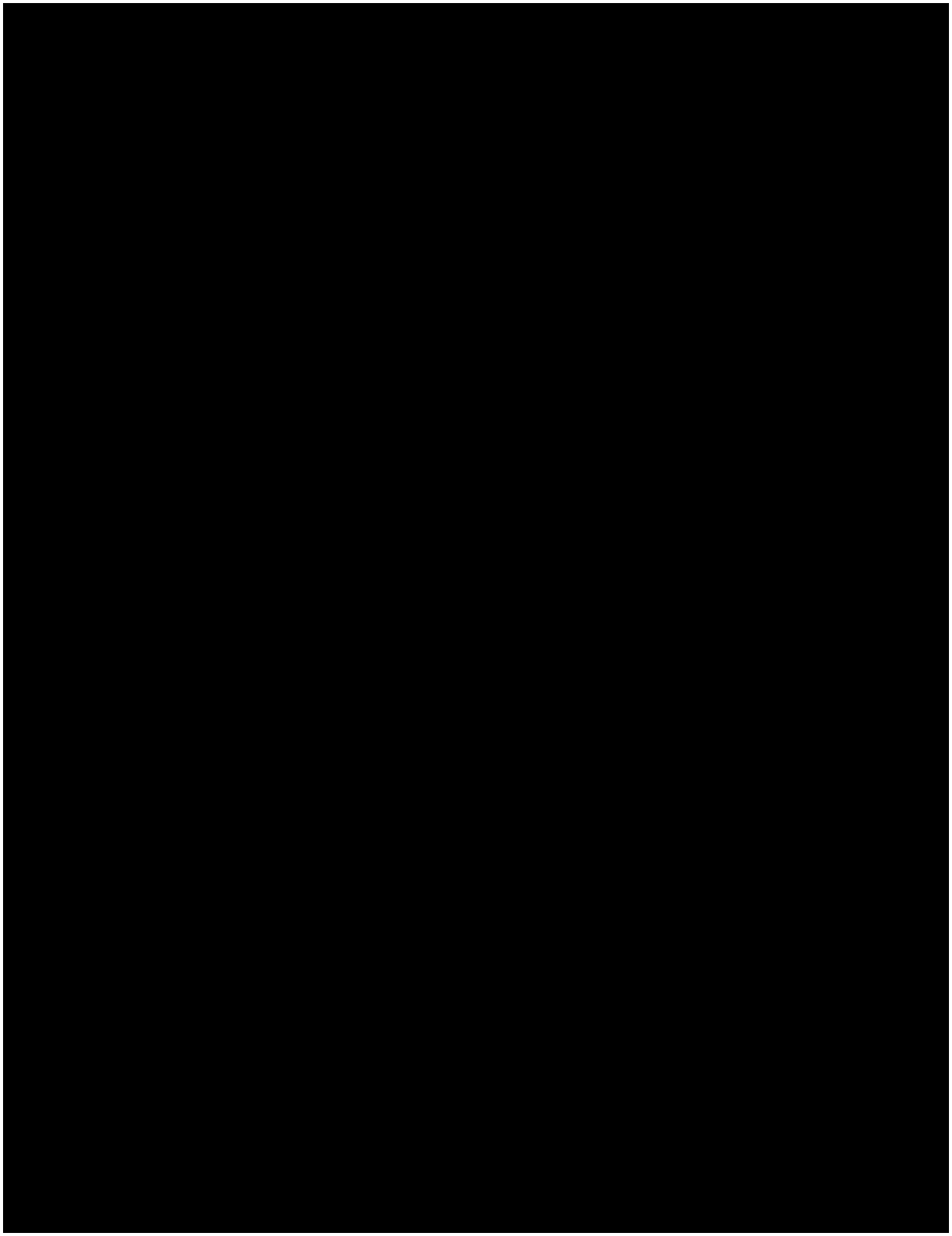
13.6.3.1 Pharmacokinetic Analysis

Blood samples will be collected from all subjects for determination of plasma concentrations of carfilzomib. Actual collection times will be recorded and used in the analysis. Individual and mean plasma concentration-versus-time data will be tabulated and plotted by dose level. The PK parameter estimates for carfilzomib will be summarized, including total plasma exposure (AUC), C_{max}, time to maximum plasma concentration (T_{max}), total plasma clearance, and plasma terminal half-life (as appropriate for data collected). Estimates for these parameters will be tabulated and summarized (ie, mean, standard deviation).

Unless otherwise specified, the PK parameter will be estimated based on noncompartmental methods. These estimates will be summarized descriptively by dose level and by single-agent or combined therapy. [redacted]

In addition to noncompartmental PK analysis, the population modeling program will be used to fit a nonlinear mixed effects model to estimate PK parameters including clearance and volume of distribution, the inter- and intra-subject variability and the population variability in the parameter estimates. The PK concentrations obtained from subjects in the Dose Escalation 1 (R3) and Dose Escalation 2 (VXLD) portions of the study, along with results from adult carfilzomib studies, will be used in the development of a structural model. The best model will be evaluated by goodness-of-fit statistics and reduction in the objective function and posterior predictive checks. Subject characteristics such as age, gender, body weight, BSA, and race will be included in the model to identify potential covariates affecting PK of carfilzomib in pediatric populations. Results from the population PK modeling will be reported separately.

[redacted]



13.7 Handling of Missing Data

Missing data for partial dates on AEs or concomitant medication may be imputed according to prespecified, conservative imputation rules. The details of the imputation rules will be defined in the statistical analysis plan.

13.8 Determination of Sample Size

The estimated sample size for the study is based on the N-CRM. A cohort size of 2 will be used and a minimum of 1 cohort (DLT-evaluable subjects) will be enrolled before the trial stops in the Dose Escalation 1 (R3) portion of the study. A cohort size of 3 will be used and a minimum of 1 cohort (DLT-evaluable subjects) will be enrolled before the trial stops in the Dose Escalation 2 (VXLD) portion. With a maximum of 18 subjects in dose escalation 1 and 24 in dose escalation 2, the algorithm was able to find MTD with reasonable probability under various dose toxicity distribution and prior assumptions based on simulation results.

14. Investigational Drug

The phase 2 protocol, including details for investigation products, is provided in Appendix K.

14.1 Carfilzomib Description, Packaging, and Storage

14.1.1 Physical Description

Carfilzomib is a synthetic small molecule peptide bearing the chemical name (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. The molecular formula is $C_{40}H_{57}N_5O_7$ and the molecular weight is 719.91.

14.1.2 Formulation

Carfilzomib for Injection will be provided as a lyophilized powder which, when reconstituted, contains a 2 mg/mL isotonic solution of carfilzomib Free Base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-beta-cyclodextrin Captisol (SBE-beta-CD).

14.1.3 Packaging and Labeling

Carfilzomib for Injection is supplied as a lyophilized parenteral product in single-use vials packaged in multivial cartons. Institutional pharmacies will be supplied with open stock vials with full-disclosure labels.

Reordering clinical drug supplies will be managed through the Interactive Voice Recognition System (IVRS) or IWRS; details are provided in the IPIM and/or the IWRS Site User Manual.

14.1.4 Storage and Stability

Study drug should be stored in a securely locked area with access limited to appropriate study personnel. Lyophilized Carfilzomib for Injection must be stored at 2°C–8°C (36°F−46°F). Vials must be kept in cartons to protect contents from light until ready for reconstitution. Additional details are provided in the IPIM.

14.2 Study Drug Accountability

The Sponsor (or designee) and the investigator will maintain records of each shipment of Carfilzomib for Injection. Upon receipt of Carfilzomib for Injection, the designated recipient at the study site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or drug accountability record. The records will document shipment dates, method of shipment, batch numbers, product presentation, quantity of vials contained in the shipment, and dispensation to individual subjects using the subject identification number.

Responsibility for drug accountability at the study site rests with the investigator; however, the investigator may assign drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities.

The investigator must ensure that the investigational products are used in accordance with the protocol. The investigator will also maintain records adequately documenting that the subjects were provided the treatment specified and reconciling all investigational products.

Remaining supplies will be retained by the pharmacy at the end of the study, and after verification of the final drug accountability by the study monitor, discarded or destroyed according to institutional Standard Operating Procedures (SOPs). Documentation of destruction of unused study medication will be maintained by the site. For each subject, the site pharmacy personnel will be required to record and document proper per protocol dispensing of carfilzomib.

14.3 Chemotherapy Backbone Description, Packaging, and Storage

Standard-of-care chemotherapy that is commercially available will not be provided or reimbursed by the Sponsor (except if required by local regulations). The investigator will be responsible for providing these agents and any ancillary supplies needed for chemotherapy administration. Administration of the chemotherapy backbone should be in accordance with the schedules provided in Sections 8.1.2 and 8.1.3.

The chemotherapy drugs used in the induction backbones (daunorubicin, dexamethasone, mitoxantrone, PEG-asparaginase, and vincristine), the chemotherapy drugs used in the consolidation backbone (6-mercaptopurine, cyclophosphamide, cytarabine, PEG-asparaginase, and vincristine), and the CNS treatment drugs (hydrocortisone, cytarabine, and methotrexate) are considered to be standard of care and are commercially available.

The description, how supplied, and storage instructions for each drug product are available in the associated prescribing information. The study staff is advised to refer to the prescribing information that is specific to the brand or formulation of the drug product being administered to subjects at their site.

14.4 Chemotherapy Backbone Accountability

Sites will be required to record and document subject compliance with the induction backbones (dexamethasone, mitoxantrone, PEG-asparaginase, and vincristine; or vincristine, dexamethasone, PEG-asparaginase, and daunorubicin), the consolidation backbone (6-mercaptopurine, cyclophosphamide, cytarabine, PEG-asparaginase, and vincristine), and the CNS treatment drugs (hydrocortisone, cytarabine, and methotrexate). Additional details are provided in the IPIM.

15. Ethical and Administrative Considerations

The phase 2 protocol, including ethical and administrative considerations, is provided in Appendix K.

15.1 Compliance Statement

This study will be conducted in accordance with the protocol and with US FDA, and the ICH Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and any applicable local health authority and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements. The investigator is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential subjects are reviewed and approved by the appropriate IRB or IEC prior to the enrollment of any study subjects.

15.2 Institutional Review Board or Independent Ethics Committee

The investigator will submit this protocol, the informed consent, IB, and any other relevant supporting information to the appropriate IRB or IEC and the local regulatory agency for review and approval prior to study initiation.

Amendments to the protocol must also be approved by the IRB/IEC and the local regulatory agency, as appropriate, prior to the implementation of changes in this study. No protocol deviations are allowed. However, the investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the study subjects without prior IRB/IEC/Sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment, should be submitted to the IRB/IEC/Sponsor. Any deviations from the protocol must be fully explained and documented by the investigator.

15.3 Informed Consent, Pediatric Assent, and Human Subject Protection

No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent and pediatric assent of the subject or the subject's legally acceptable representative. An investigator shall seek such consent and assent only under circumstances that provide the prospective subject or the subject's legally acceptable representative sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in a language understandable to the subject or representative.

The Sponsor or its designated representative will provide the investigator with sample consent and assent forms. Local and/or institutional requirements may require disclosure of additional information in the ICF. Any changes to the consent or assent forms must be submitted to the sponsor or its designated representative for acceptance, prior to submission to the IRB/IEC. The IRB/IEC will review the consent and assent forms for approval. A copy of the approved forms must be submitted to the sponsor or its designated representative for its approval prior to initiation of the study. Before implementing any study procedure on a particular subject, informed consent and assent shall be documented in such subject's case histories and by the use of written consent and assent forms approved by the Sponsor and the IRB/IEC and signed and dated by the subject or the subject's legally acceptable representative at the time of consent and assent. Copies of the signed informed consent and assent forms will be given to the subject or subject's legally acceptable representative. The original signed consent and assent forms must be maintained by the investigator and available for inspection by the

Sponsor, its designated representative, or regulatory authority representatives at any time.

15.4 Direct Access to Source Data, Source Documents, and Study Records

The study will be carried out in keeping with applicable local laws and regulations. This may include an inspection by Sponsor representatives/designees, and/or regulatory authority representatives at any time. The investigator/institution must agree to the inspection of study-related records by the regulatory authority/Sponsor representatives/designees and must allow direct access to source documents to the regulatory authority/Sponsor representatives/designees/IRB/IEC. The investigator must allocate time (investigator and study staff) to discuss findings and relevant issues with the regulatory authority/Sponsor representatives.

15.5 Data Collection and Handling

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs (or paper Case Report Forms [CRFs]) and source documentation as part of the case histories. These source documents may include subject diaries, laboratory reports, and other documents. The Sponsor will supply the eCRF (or CRF), which will be completed in English.

Data collection will involve the use of the EDC system, to which only authorized personnel will have access.

The investigator or designee must enter all results collected during the clinical study into eCRFs (or CRFs). Guidelines for completion of eCRFs (or CRFs) will be reviewed with study site personnel at the site initiation visits. Investigators are responsible for approval of the entered/corrected data. Detailed instructions may be found in the other study-specific documents.

All entries made on the eCRF (or CRF), must be verifiable against source documents. In addition to periodic monitoring occurring within the system by study monitors, programmatic edit checks and data listings will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be electronically issued to the clinical study sites and electronically resolved by those sites.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to assure subject confidentiality in accordance with the legal and regulatory requirements applying to protected health information. Study records (eg, copies of eCRFs, regulatory documents) will be retained at the study site, along with adequate source documentation. The study file and all source data should be retained for the time period required by applicable regulatory requirements and will not be destroyed until written notification is given by the sponsor or designee for destruction.

15.6 Confidentiality

All records identifying the subject will be kept confidential and, in accordance with the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded on the CRF. If the subject name appears on any other document (eg, pathologist report) or study materials (eg, biopsy tissue slides), then that information must be redacted before a copy of the document is supplied to the sponsor. Study data stored on a computer will be stored in accordance with local data protection laws and regulations. Subjects will be informed in writing that representatives of the sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws and regulations.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified in accordance with applicable laws and regulations and according to the terms and agreed upon in such subjects' signed consent forms.

15.7 Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does

not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

16. References

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17. Appendices

17.1 Appendix A. Schedule and Description of Assessments, Screening for Phase 1

Schedule of Screening Assessments

Assessment	Up to 72 Hours Before Enrollment	Up to 7 Days Before Enrollment
Complete history and physical examination	X	
Bone marrow aspirate		X[a]
Lumbar puncture		X
Examination for testicular involvement		X
ECG (12-lead)		X
Echocardiogram (fractional shortening)		X
Local laboratory evaluations:		
CBC with differential and platelet count	X	
Serum electrolytes: Na, K, Cl, CO_2, Ca, Mg, P	X	
Blood glucose	X	
Renal function: BUN, Cr; NM-GFR only if Cr ≥1.5 x ULN	X	
Hepatic function: AST, ALT, total and direct bilirubin, ALP, albumin	X	
Pancreatic function: amylase, lipase	X	
Uric acid	X	
Serum or urine pregnancy test, females of reproductive potential	X	
Hepatitis B testing		X[b]

anti-HBs = hepatitis B surface antibody; CBC = complete blood count; ECG = electrocardiogram; HBV = hepatitis B virus; ULN = upper limit of normal.

[redacted]

An ICF and, where applicable, a pediatric assent form must be signed before any study-specified tests may be performed.

A complete history and physical examination must include all of the following:

- Review of medical and surgical histories, including:
  - Prior cumulative anthracycline exposure
  - Known or suspected cancer pre-disposition syndromes
  - Other co-morbidities which, in the investigator's opinion, either place a subject at increased risk for adverse events, or have potential impact on the results of study-specified tests, including, but is not limited to: Endocrinopathies, gastrointestinal disorders, inborn errors of metabolism, congenital heart disease (repaired or unrepaired), epilepsy.
  - Documentation of all current medications
- Vital signs: temperature, heart rate, respiratory rate, systolic and diastolic blood pressures
- Weight, height, and body surface area
- Performance status assessment: Lansky score if <16 years of age; Karnofsky score if ≥16 years of age
- Examination of all of the following: head, ears, eyes, nose, oropharynx, neck, heart, lungs, abdomen, genitalia, back, extremities, lymph nodes, skin, nervous system
- Determination of the baseline NCI-CTCAE (Version 4.03) grade for all abnormal physical examination findings

Bone marrow aspirate must be obtained and a morphologic diagnosis of relapsed or refractory acute lymphoblastic leukemia must be determined prior to study enrollment. In the event that aspirate cannot be obtained, diagnosis may be made by biopsy. It is not necessary for the results of immunophenotyping or cytogenetic studies to be available prior to enrollment or the initiation of study treatment.

[redacted]

Cerebrospinal fluid must be obtained prior to the initiation of study treatment and examination must include: RBC count, WBC count, differential, cytology.

for other assessments.

b Hepatitis serologies may be obtained up to 2 weeks prior to enrollment. Testing is not required if tested negative within 6 months of screening and no change in the subject's risk factors within these 6 months. Subjects with positive testing or a history of prior HBV infection should have consultation with a specialist and must have HBV-DNA testing at screening and again at safety follow up. Subjects that have received hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV-DNA monitoring.

17.2 Appendix B. Schedule and Description of Assessments, Lead-in Window for Phase 1

On-Study Assessments: Lead-in Window

Assessment	Cycle Day 1	Cycle Day 2	Cycle Day 8
Physical examination	X		X
Lumbar puncture			
CNS- negative	X[a]		X
CNS- positive	X[a]		X
Local laboratory evaluations			
CBC with differential and platelet count	X[a]		X
Electrolytes: Na, K, Cl, CO_2, Ca, Mg, P	X[a]		X
Blood glucose	X[a]		X
Renal function: BUN, Cr	X[a]		X
Hepatic function: AST, ALT, total and direct bilirubin, ALP, albumin	X[a]		X
Pancreatic function: amylase, lipase	X[a]		X
Uric acid	X[a]		X
Bone-specific ALP	X		
Correlative study measurements			
Pharmacokinetic studies	X		
[redacted]	[redacted]	[redacted]	
[redacted])	[redacted]		[redacted]
Response assessment/bone marrow aspirate (including MRD)			X

[a] Assessments from the screening period must have been obtained within 72 hours before enrollment (or for lumbar puncture, within 7 days before enrollment) and no repeat Day 1 study assessments are required, except for repeat evaluations of the blood when the initiation of study treatment occurs >48 hours after these labs were obtained or at the discretion of the investigator.

[redacted]

Physical examination during study treatment must include all of the following:

- Updated documentation of all current medications
- Weight, height, and body surface area
- Vital Signs: temperature, heart rate, respiratory rate, and systolic and diastolic blood pressures
- Examination of all of the following: head, ears, eyes, nose, oropharynx, heart, lungs, abdomen, extremities, lymph nodes, skin, and nervous system
- Determination of the updated CTCAE (v. 4.03) grade for all abnormal physical examination findings. Clinically significant abnormal findings that are new or represent a worsening after the signature of the ICF must be reported as AEs.

Local laboratory evaluations of the blood must be obtained and results reviewed prior to the delivery of study treatment and may be obtained as early as 48 hours in advance. The blood sample for bone-specific ALP must be collected prior to the initiation of study treatment.

Blood samples for PK studies must be collected from all subjects for determination of plasma concentrations of carfilzomib at the following time points: predose; 15 minutes after the start of infusion; immediately (within 2 minutes before the end of infusion); and at 10 minutes, 30 minutes, and 1, 2, and 4 hours after the end of the infusion.

Blood samples for PDn studies must be collected predose and approximately 1 hour following the Day 1 and Day 2 carfilzomib dose.

[redacted]

Response assessment includes physical examination, CBC, lumbar puncture, and bone marrow aspiration. A lumbar puncture is not required after the second lumbar puncture for subjects who are CNS-negative. CNS-positive subjects must have 2 consecutive lumbar punctures without evidence of leukemia, before lumbar puncture is no longer required.

17.3 Appendix C. Schedule and Description of Assessments, Induction for Phase 1

On-Study Assessments: Induction Cycle

Assessment	Cycle Day 1	2	8	15	22	29	35	42
Physical examination	X[a]		X	X	X	X		
Lumbar puncture (CNS-negative)								
Dose Escalation 1 (R3)	X							
Dose Escalation 2 (VXLD)	X[a]		X					
Lumbar puncture (CNS-positive)								
Dose Escalation 1 (R3)	X		X	X		X		
Dose Escalation 2 (VXLD)	X[a]		X	X	X	X		
Local laboratory evaluations								
CBC with differential and platelet count	X[a]		X	X	X	X	X[d]	X[d]
Electrolytes: Na, K, Cl, CO_2, Ca, Mg, P	X[a]		X	X	X	X		
Blood glucose	X[a]		X	X	X	X		
Renal function: BUN, Cr	X[a]		X	X	X	X		
Hepatic function: AST, ALT, total and direct bilirubin, ALP, albumin	X[a]		X	X	X	X		X[d]
Pancreatic function: amylase, lipase	X[a]		X	X	X	X		
Uric acid	X[a]		X	X	X	X		
Bone-specific ALP	X[b]					X		
Correlative study measurements								
Pharmacokinetic studies			X					
[redacted]	[redacted]	[redacted][b]				[redacted]		
Response assessment/bone marrow aspirate (including MRD)						X		

[a] For subjects in the Dose Escalation 2 (VXLD) portion of the study, assessments from the screening period must have been obtained within 72 hours before enrollment (or for lumbar puncture, within 7 days before enrollment) and no repeat Day 1 study assessments are required, except repeat assessments of the blood when the initiation of study treatment occurs >48 hours after these labs were obtained or at the discretion of the investigator.

[redacted]

[d] Laboratory assessments after day 29 of induction should be collected up to start of consolidation.

Physical examination during study treatment must include all of the following:

- Updated documentation of all current medications
- Weight, height, and body surface area
- Vital Signs: temperature, heart rate, respiratory rate, and systolic and diastolic blood pressures
- Examination of all of the following: head, ears, eyes, nose, oropharynx, heart, lungs, abdomen, extremities, lymph nodes, skin, and nervous system
- Determination of the updated CTCAE (v. 4.03) grade for all abnormal physical examination findings. Clinically significant abnormal findings that are new or represent a worsening after the signature of the ICF must be reported as AEs.

Local laboratory evaluations of the blood must be obtained and results reviewed prior to the delivery of study treatment and may be obtained as early as 48 hours in advance. The first blood sample for bone-specific ALP must be collected prior to the initiation of study treatment. Laboratory assessments after day 29 of induction should be collected up to start of consolidation.

Blood samples for PK studies must be collected from all subjects for determination of plasma concentrations of carfilzomib at the following time points: predose; 15 minutes after the start of infusion; immediately (within 2 minutes before the end of infusion); and at 10 minutes, 30 minutes, and 1, 2, and 4 hours after the end of the infusion.

Blood samples for PDn studies must be collected predose and approximately 1 hour following the Day 1 and Day 2 carfilzomib dose and once on Day 29 of induction

[redacted]

normal DNA for the Dose Escalation 2 (VXLD) portion of the study only (not Dose Escalation 1 [R3]).

Response assessment includes physical examination, CBC, lumbar puncture, and bone marrow aspiration. A lumbar puncture is not required after the second lumbar puncture for subjects who are CNS-negative. CNS-positive subjects must have 2 consecutive lumbar punctures without evidence of leukemia, before lumbar puncture is no longer required.

17.4 Appendix D. Schedule and Description of Assessments, Optional Consolidation for Phase 1

On-Study Assessments: Optional Consolidation Cycle

	Cycle Day				
Assessment	**1**	**8**	**15**	**22**	**29**
Physical examination	X	X	X	X	X
Lumbar puncture					
CNS- negative	X	X	X	X	
CNS- positive	X	X	X	X	X[a]
Local laboratory evaluations					
CBC with differential and platelet count	X	X	X	X	X
Electrolytes: Na, K, Cl, CO_2, Ca, Mg, P	X	X	X	X	X
Blood glucose	X	X	X	X	X
Renal function: BUN, Cr	X	X	X	X	X
Hepatic function: AST, ALT, total and direct bilirubin, ALP, albumin	X	X	X	X	X
Pancreatic function: amylase, lipase	X	X	X	X	X
Response assessment/bone marrow aspirate (including MRD)					X

[a] Required only for subjects who remain CNS-positive on Day 22.

A new ICF and, where applicable, a new pediatric assent form is required for participation in this cycle.

Physical examination during study treatment must include all of the following:

- Updated documentation of all current medications
- Weight, height, and body surface area
- Vital Signs: temperature, heart rate, respiratory rate, and systolic and diastolic blood pressures
- Examination of all of the following: head, ears, eyes, nose, oropharynx, heart, lungs, abdomen, extremities, lymph nodes, skin, and nervous system
- Determination of the updated CTCAE (v. 4.03) grade for all abnormal physical examination findings. Clinically significant abnormal findings that are new or represent a worsening after the signature of the ICF must be reported as AEs

Local laboratory evaluations of the blood must be obtained and results reviewed prior to the delivery of study treatment and may be obtained as early as 48 hours in advance.

Response assessment includes physical examination, CBC, lumbar puncture, and bone marrow aspiration. A lumbar puncture is not required after the second lumbar puncture for subjects who are CNS-negative. CNS-positive subjects must have 2 consecutive lumbar punctures without evidence of leukemia, before lumbar puncture is no longer required.

17.5 Appendix E. Description of End--of-study Assessments for Phase 1

End-of-Study Assessments

Assessment	30 Days (± 4 Days) After Last Dose of Study Treatment
Physical examination	X
Local laboratory evaluations	X
CBC with differential and platelet count	X
Electrolytes: Na, K, Cl, CO_2, Ca, Mg, P	X
Blood glucose	X
Renal function: BUN, Cr	X
Hepatic function: AST, ALT, total and direct bilirubin, ALP, albumin	X
Hepatitis B testing	X[a]
Pancreatic function: amylase, lipase	X

HBV = hepatitis B virus

[a] Only in subjects with positive hepatitis B serology at screening or past history of HBV infection.

A complete history and physical examination must include all of the following:

- Review of medical and surgical histories, including documentation of all current medications
- Vital Signs:
  - Temperature
  - Heart rate
  - Respiratory rate
  - Systolic and diastolic blood pressures
- Weight, height, and body surface area
- Performance status assessment:
  - Lansky score if < 16 years of age
  - Karnofsky score if ≥ 16 years of age
- Examination of all of the following:
- Head, ears, eyes, nose, oropharynx, neck, heart, lungs, abdomen, genitalia, back, extremities, lymph nodes, skin, nervous system.
- Determination of the updated NCI-CTCAE (Version 4.03) grade for all abnormal physical examination findings.

The End-of-Study Assessments must be completed 30 days (± 4 days) following the last dose of study treatment. For subjects who complete the End-of-Study Assessment less than 30 ± 4 days following the last dose of study treatment, a follow-up of ongoing AEs should be attempted by telephone and documented in the subject's source file. All AEs must be followed until resolution, unless the investigator has determined that the event has stabilized or is not expected to improve.

17.6 Appendix F. Karnofsky and Lansky Performance Status Scales

Performance Status Criteria

Karnofsky and Lansky performance scores are intended to be multiples of 10.

Karnofsky		Lansky	
Score	**Description**	**Score**	**Description**
100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort, some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self. Unable to carry on normal activity or to do active work.	70	Both greater restriction of, and less time spent in, active play.
60	Requires occasional assistance, but is able to care for most of his needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization is indicated although death not imminent.	30	In bed; needs assistance even for quiet play.
20	Hospitalization necessary, very sick, active supportive treatment necessary.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.
0	Dead.	0	Unresponsive.

Sources: Karnofsky 1949; Lansky 1987.

17.7 Appendix G. Guidance for Determining Previous Cumulative Anthracycline Dose

Total Anthracycline Calculation Worksheet

Instructions:

In order to calculate the total anthracycline received by a subject, you will need to review the subject's previous treatment. You will need to document each dose of anthracycline chemotherapy prescribed and received by the subject.

Step 1: Indicate which drug the subject received. (Contact the investigator if drug not listed)

Step 2: Enter the prescribed dose for that drug per the chemotherapy roadmap/orders. Be sure to list all doses.

Step 3: Enter the corresponding conversion factor for the drug given.

Step 4: Multiply the prescribed dose by the conversion factor and enter the result in the Total Anthracycline column.

Step 5: After you have completed this worksheet for all doses, add all the total doses to obtain the Total Cumulative Dose.

Drug	**Prescribed Dose** The prescribed dose is the dose of chemotherapy written in the protocol. It will be listed as mg/m^2. (It is not the actual dose received by the subject)	**Conversion Factor** Doxorubicin = 1 Daunorubicin = 0.5 Idarubicin = 2.5 Mitoxantrone = 2.5	Total Anthracycline
EXAMPLE:			
☐ Doxorubicin ☐ Daunorubicin ☒ Idarubicin ☐ Mitoxantrone	***10 mg/m^2***	***2.5***	***25 mg/m^2***
☐ Doxorubicin ☐ Daunorubicin ☐ Idarubicin ☐ Mitoxantrone			
☐ Doxorubicin ☐ Daunorubicin ☐ Idarubicin ☐ Mitoxantrone			
☐ Doxorubicin ☐ Daunorubicin ☐ Idarubicin ☐ Mitoxantrone			
☐ Doxorubicin ☐ Daunorubicin ☐ Idarubicin ☐ Mitoxantrone			
☐ Doxorubicin ☐ Daunorubicin ☐ Idarubicin ☐ Mitoxantrone			
		Total Cumulative Dose	

17.8 Appendix H. Sample Serious Adverse Event Report Form

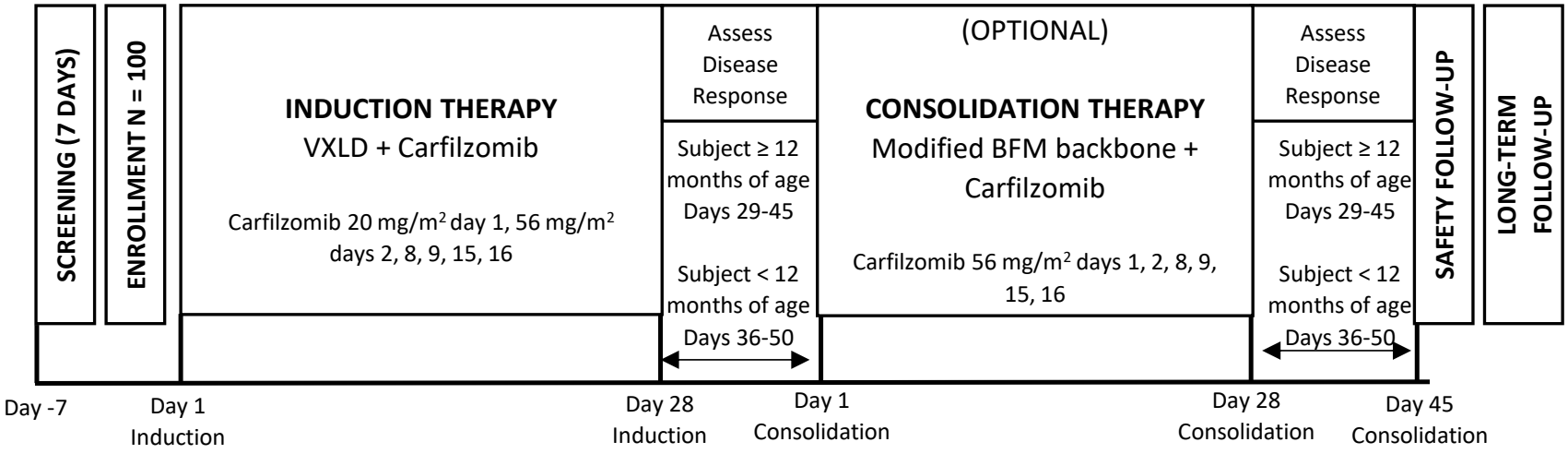
Phase 1b of the study is closed. See Section 28 Figure 6 for phase 2 serious adverse event report forms.

17.9 Appendix I. Pregnancy Notification Form

Phase 1b of the study is closed. See Section 29 Figure 7 for phase 2 Pregnancy Notification Form.

17.10 Appendix J. Lactation Notification Worksheet

Phase 1b of the study is closed. See Section 29 Figure 7 for phase 2 Lactation Notification Form.


SCREENING (7 DAYS)
ENROLLMENT N = 100
INDUCTION THERAPY
VXLD + Carfilzomib
Carfilzomib 20 mg/m2 day 1, 56 mg/m2 days 2, 8, 9, 15, 16
Assess Disease Response
Subject ≥ 12 months of age Days 29-45
Subject < 12 months of age Days 36-50
(OPTIONAL)
CONSOLIDATION THERAPY
Modified BFM backbone + Carfilzomib
Carfilzomib 56 mg/m2 days 1, 2, 8, 9, 15, 16
Assess Disease Response
Subject ≥ 12 months of age Days 29-45
Subject < 12 months of age Days 36-50
SAFETY FOLLOW-UP
LONG-TERM FOLLOW-UP
Day -7
Day 1 Induction
Day 28 Induction
Day 1 Consolidation
Day 28 Consolidation
Day 45 Consolidation

17.11.2 Phase 2: Schedule of Activities, Phase 2

Table 14. Phase 2 Schedule of Activities – Induction Therapy Subjects Greater Than or Equal to 12 Months of Age at Screening

	Screening[e]	Treatment Period (Induction Therapy Subjects Greater Than or Equal to 12 Months of Age)										SFU[a]	LTFU (every 12 weeks)[b]	Comments
Study Day	**(up to 7 days before day 1)**	**1**	**2**	**4**	**8**	**9**	**15**	**16**	**18**	**22**	**29-45[c]**			
General and Safety Assessments														
Informed consent and assent	X													
Inclusion and exclusion criteria	X													
Demographics	X													
Physical examination	X											X		
Physical measurements	X											X		Weight and height at screening; weight at SFU
Medical history	X													
Substance use history	X													Includes tobacco exposure
ECG[e]	X													
ECHO[e]	X										X			Subjects with clinical symptoms of congestive heart failure during or after induction should have an ECHO to evaluate cardiac function before initiation of the optional consolidation.
Vital signs	X	X			X		X			X	X	X		Temperature, heart rate, respiratory rate, and systolic and diastolic blood pressures. On days 29 to 45, assessment only required at time of bone marrow assessment.
Karnofsky or Lansky Performance status	X											X		Lansky if less than 16 years of age; Karnofsky if greater than or equal to 16 years of age
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X		Collected from time of signing of the ICF. Details regarding the reporting of adverse events are provided in Section 24.2.4.

	Screening[e]	Treatment Period (Induction Therapy Subjects Greater Than or Equal to 12 Months of Age)										SFU[a]	LTFU (every 12 weeks)[b]	Comments
Study Day	**(up to 7 days before day 1)**	**1**	**2**	**4**	**8**	**9**	**15**	**16**	**18**	**22**	**29-45[c]**			
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	Collected from time of signing of the ICF. Details regarding the reporting of serious adverse events are provided in Section 24.2.4.
Concomitant therapies review	X	X	X	X	X	X	X	X	X	X	X	X		Collected from time of signing of the ICF. Details regarding the reporting of concomitant therapies are provided in Section 22.7.2.
LABORATORY ASSESSMENTS														
Pregnancy test (females of childbearing potential only)[e]	X													Serum or urine. Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.
Coagulation[e]	X													INR, aPTT
Hematology[e]	X	X			X		X			X	X	X		See Table 28 for analytes. On days 29 to 45, assessment to be performed weekly, at the time of bone marrow assessment, and on day 45 in subjects that have not yet proceeded to next therapy. Samples obtained on day of bone marrow and within 1 week after the bone marrow will be assessed locally and a stained slide must be sent to central lab, unless subject has already started next therapy at the time the sample is obtained.
Chemistry[e]	X	X			X		X			X	X	X		See Table 28 for analytes. In addition to chemistries in the complete metabolic panel, include adjusted calcium, ALP, magnesium, phosphorous, serum albumin, and total protein if not part of standard panel; direct bilirubin if total bilirubin is elevated; and uric acid until normalized for 2 consecutive measurements. On days 29 to 45, assessment only required at time of bone marrow assessment.
Pancreatic function[e]	X										X	X		Amylase and lipase

	Screening[e]	Treatment Period (Induction Therapy Subjects Greater Than or Equal to 12 Months of Age)										SFU[a]	LTFU (every 12 weeks)[b]	Comments
Study Day	**(up to 7 days before day 1)**	**1**	**2**	**4**	**8**	**9**	**15**	**16**	**18**	**22**	**29-45[c]**			
Hepatitis B screening[e]	X											X[d]		All hepatitis testing will be performed locally. All subjects will be tested at screening for HBsAg, anti-HBs, and anti-HBc, unless testing was previously performed within 6 months of screening and there was no change in the subject's risk factors within these 6 months.
CMV PCR testing[e]	X													Recommended for all subjects, but only required for subjects who are known to be CMV positive or who previously received a bone marrow transplant.
STUDY-SPECIFIC ASSESSMENTS														
Bone marrow aspirate/biopsy[e]	X										X			On days 29 to 45, perform assessment when peripheral blood counts recover (defined as ANC greater than or equal to 1000/μL, platelets greater than or equal to 100 000/μL) or as clinically indicated, to assess for CR, by day 45, or as clinically indicated. MRD BMA using NGS has priority over MRD BMA flow cytometry or PCR. Bone marrow will be assessed locally and stained slides will be submitted to central laboratory for histological examination.
Lumbar puncture with or without IT[e]	X	X			X		X			X	X			If IT therapy is administered during screening (within 7 days of day 1), repeat of IT on day 1 is not required. Lumbar puncture performed on days 15 and 22 only if CNS3 (Table 3). On days 29 to 45, assessment only required at time of bone marrow assessment.
Testicular ultrasound/physical exam (males with testicular mass only)[e]	X										X			Remission is to be determined by the same technique used at screening

	Screening[e]	Treatment Period (Induction Therapy Subjects Greater Than or Equal to 12 Months of Age)										SFU[a]	LTFU (every 12 weeks)[b]	Comments
Study Day	**(up to 7 days before day 1)**	**1**	**2**	**4**	**8**	**9**	**15**	**16**	**18**	**22**	**29-45[c]**			
Chest imaging (only required if mediastinal mass is present at screening)	X										X			On days 29 to 45, assessment, by same technique as at screening, only required at time of bone marrow assessment.
Other extramedullary disease assessment[e]	X										X			Only if clinically indicated, response should be assessed using same method used at screening
Vital Status													X	
Subsequent ALL therapy													X	Collect if relapsed (yes, no). If relapsed was subsequent ALL therapy administered? If yes, what therapy?
[redacted]														
[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]			[redacted]
PHARMACOKINETIC ASSESSMENTS														
Pharmacokinetic blood samples		X			X									Day 1: predose and within 2 min before EOI; Day 8: predose, 15 min after the start of infusion, within 2 min before EOI; and 15, 60, and 120 min after EOI

ALL = acute lymphoblastic leukemia; ALP = alkaline phosphatase; ANC = absolute neutrophil count; anti-HBs = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; aPTT = activated partial thromboplastin time; BMA = bone marrow aspirate; CMV = cytomegalovirus; CNS = central nervous system; CR = complete remission; ECG = electrocardiogram; ECHO = echocardiogram; EOI = end of infusion; HBsAg = hepatitis B surface antigen; ICF = informed consent; INR = international normalized ratio; IT = intrathecal therapy; LTFU = long term follow-up; MRD = minimal residual disease; NGS = next generation sequencing; PCR = polymerase chain reaction; SFU = safety follow-up

[a] The safety follow-up visit is to be performed 30 days after the last dose of protocol specified systemic anti-leukemia therapy in induction or consolidation whichever is later, or prior to next therapy following induction if not proceeding to optional consolidation, or prior to next therapy after consolidation.

[b] After the safety follow-up visit, subjects are to continue follow-up every 12 weeks for up to 2 years.

[c] The timing of assessments on days 29 to 45 and when/if a subject proceeds to the consolidation phase is to be determined by the investigator based on the subject's peripheral blood count recovery or the start of alternate therapy, whichever comes first. Assessments may be repeated multiple times within this window at the discretion of the investigator as needed to assess for response or progression. If peripheral blood counts recover within 7 days of an M1 bone marrow assessment a repeat bone marrow is not required to confirm CR.

[d] Subjects with positive testing or a history of prior HBV infection should have consultation with a specialist and must have HBV-DNA testing at screening and again at safety follow-up. Subjects that have received hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV-DNA monitoring.

[e] Evaluations performed within 7 days of enrollment as part of routine medical care (eg, bone marrow aspirate/biopsy) may be used for screening assessments.

Table 15. Phase 2 Dosing Regimen for Induction Therapy – Subjects Greater Than or Equal to 12 Months of Age at Screening

	Screening	Treatment Period (Induction Therapy Subjects Greater Than or Equal to 12 Months of Age)										Comments
Study Day	**(up to 7 days before day 1)**	**1**	**2**	**4**	**8**	**9**	**15**	**16**	**18**	**22**	**29-45**	
STUDY TREATMENT												
Carfilzomib		X	X		X	X	X	X				20 mg/m^2 on day 1, 56 mg/m^2 for subsequent doses. Administer IV over 30 $\pm$ 5 minutes
Prehydration		X	X		X	X	X	X				Greater than or equal to 125 mL/m^2/hour of IV fluid is required for 1 hour prior to carfilzomib administration
Vincristine		X			X		X			X		1.5 mg/m^2 per dose (maximum single dose 2 mg). Administer as IV push over 1 min or infusion per institutional policy.
Dexamethasone		X	X	X	X	X	X	X	X			3 mg/m^2 per dose twice daily (total daily dose 6 mg/m^2) on days 1 through 21. Administer orally or as IV. Given 4 hours to 30 minutes prior to carfilzomib doses. See Section 22.1.2.1 for acceptable alternatives.
PEG-asparaginase				X					X			2500 U/m^2 per dose. Administer IV. See Section 22.1.2.1 for acceptable alternatives.
Daunorubicin			X									60 mg/m^2 per dose. Administer as an infusion over 15 to 60 minutes per institutional practice. See Section 22.1.2.1 for acceptable alternatives.
IT – CNS Negative at Screening	X				X						day 29	Methotrexate, dose is age dependent (see Figure 3). IT therapy may be performed on day 29 per institutional standard practice. See Section 22.1.4 for acceptable alternatives.
IT – CNS Positive (CNS 3) at Screening	X				X		X			X	day 29	Methotrexate, cytarabine, and hydrocortisone doses are age dependent (see Figure 3). IT therapy may be performed on day 29 per institutional standard practice. See Section 22.1.4 for acceptable alternatives.

CNS = central nervous system; IT = intrathecal therapy; IV = intravenous; PEG = polyethylene glycol

Table 16. Phase 2 Schedule of Activities – Induction Therapy Subjects Less Than 12 Months of Age at Screening

	Screening[e]	Treatment Period (Induction Therapy Subjects Less Than 12 Months of Age)																SFU[a]	LTFU (every 12 weeks)[b]	
Study Day	**(up to 7 days before day 1)**	**1**	**2**	**3-7**	**8**	**9**	**10-11**	**12**	**13-14**	**15**	**16**	**17-21**	**22**	**23-27**	**28**	**29**	**36-50[c]**			**Comments**
GENERAL AND SAFETY ASSESSMENTS																				
Informed consent and assent	X																			
Inclusion and exclusion criteria	X																			
Demographics	X																			
Physical examination	X																	X		
Physical measurements	X																	X		Weight and height at screening; weight at SFU
Medical history	X																			
Substance use history	X																			Includes tobacco exposure
ECG[e]	X																			
ECHO[e]	X																X			Subjects with clinical symptoms of congestive heart failure during or after induction should have an ECHO to evaluate cardiac function before initiation of the optional consolidation.

	Screening[e]	Treatment Period (Induction Therapy Subjects Less Than 12 Months of Age)																SFU[a]	LTFU (every 12 weeks)[b]	
Study Day	**(up to 7 days before day 1)**	**1**	**2**	**3-7**	**8**	**9**	**10-11**	**12**	**13-14**	**15**	**16**	**17-21**	**22**	**23-27**	**28**	**29**	**36-50[c]**			**Comments**
Vital signs	X	X			X					X			X				X	X		Temperature, heart rate, respiratory rate, and systolic and diastolic blood pressures. On days 36 to 50, assessment only required at time of bone marrow assessment.
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Collected from time of signing of the ICF. Details regarding the reporting of adverse events are provided in Section 24.2.4.
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Collected from time of signing of the ICF. Details regarding the reporting of serious adverse events are provided in Section 24.2.4.
Concomitant therapies review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Collected from time of signing of the ICF. Details regarding the reporting of concomitant therapies are provided in Section 22.7.2.
LABORATORY ASSESSMENTS																				
Coagulation[e]	X																			INR, aPTT

	Screening[e]	Treatment Period (Induction Therapy Subjects Less Than 12 Months of Age)																SFU[a]	LTFU (every 12 weeks)[b]	
Study Day	(up to 7 days before day 1)	1	2	3-7	8	9	10-11	12	13-14	15	16	17-21	22	23-27	28	29	36-50[c]			Comments
Hematology[e]	X	X			X					X			X			X	X	X		See Table 28 for analytes. On days 36 to 50, assessment to be performed weekly starting on day 36, at the time of bone marrow assessment, and on day 50 in subjects that have not yet proceeded to next therapy, samples obtained on day of bone marrow and within 1 week after the bone marrow will be assessed locally and a stained slide must be sent to central lab, unless subject has already started next therapy at the time the sample is obtained.

	Screening[e]	Treatment Period (Induction Therapy Subjects Less Than 12 Months of Age)																SFU[a]	LTFU (every 12 weeks)[b]	
Study Day	**(up to 7 days before day 1)**	**1**	**2**	**3-7**	**8**	**9**	**10-11**	**12**	**13-14**	**15**	**16**	**17-21**	**22**	**23-27**	**28**	**29**	**36-50[c]**			**Comments**
Chemistry[e]	X	X			X					X			X			X	X	X		See Table 28 for analytes. In addition to chemistries in the complete metabolic panel, include adjusted calcium, ALP, magnesium, phosphorous, serum albumin, and total protein if not part of standard panel; direct bilirubin if total bilirubin is elevated; and uric acid until normalized for 2 consecutive measurements. On days 36 to 50, assessment only required at time of bone marrow assessment.
Pancreatic function[e]	X																X	X		Amylase and lipase

	Screening[e]	Treatment Period (Induction Therapy Subjects Less Than 12 Months of Age)																SFU[a]	LTFU (every 12 weeks)[b]	
Study Day	(up to 7 days before day 1)	1	2	3-7	8	9	10-11	12	13-14	15	16	17-21	22	23-27	28	29	36-50[c]			Comments
Hepatitis B screening[e]	X																	X[d]		All hepatitis testing will be performed locally. All subjects will be tested at screening for HBsAg, anti-HBs, and anti-HBc, unless testing was previously performed within 6 months of screening and there was no change in the subject's risk factors within these 6 months.
CMV PCR testing[e]	X																			Recommended for all subjects, but only required for subjects who are known to be CMV positive or who previously received a bone marrow transplant.

	Screening[e]	Treatment Period (Induction Therapy Subjects Less Than 12 Months of Age)																SFU[a]	LTFU (every 12 weeks)[b]	
Study Day	**(up to 7 days before day 1)**	**1**	**2**	**3-7**	**8**	**9**	**10-11**	**12**	**13-14**	**15**	**16**	**17-21**	**22**	**23-27**	**28**	**29**	**36-50[c]**			**Comments**
STUDY-SPECIFIC ASSESSMENTS																				
Bone marrow aspirate/biopsy[e]	X																X			On days 36 to 50, perform assessment when peripheral blood counts recover (defined as ANC greater than or equal to 1000/μL, platelets greater than or equal to 100 000/μL) or as clinically indicated, to assess for CR, by day 50, or as clinically indicated. MRD BMA using NGS has priority over MRD BMA flow cytometry or PCR. Bone marrow will be assessed locally and stained slides will be submitted to central laboratory for histological examination.

	Screening[e]	Treatment Period (Induction Therapy Subjects Less Than 12 Months of Age)																SFU[a]	LTFU (every 12 weeks)[b]	
Study Day	**(up to 7 days before day 1)**	**1**	**2**	**3-7**	**8**	**9**	**10-11**	**12**	**13-14**	**15**	**16**	**17-21**	**22**	**23-27**	**28**	**29**	**36-50[c]**			**Comments**
Lumbar puncture with or without IT[e]	X	X								X						X	X			If IT therapy is administered during screening (within 7 days of day 1) repeat of IT on day 1 is not required. On days 36 to 50, assessment only required at time of bone marrow assessment.
Testicular ultrasound/physical exam (males with testicular mass only)[e]	X																X			Remission is to be determined by the same technique used at screening
Chest imaging (if mediastinal mass is present at screening only)[e]	X																X			On days 36 to 50, assessment, by same technique as at screening, only required at time of bone marrow assessment.
Other extramedullary disease assessment[e]	X																X			Only if clinically indicated, response should be assessed using same method used at screening
Vital status																			X	

	Screening[e]	Treatment Period (Induction Therapy Subjects Less Than 12 Months of Age)																SFU[a]	LTFU (every 12 weeks)[b]	
Study Day	(up to 7 days before day 1)	1	2	3-7	8	9	10-11	12	13-14	15	16	17-21	22	23-27	28	29	36-50[c]			Comments
Subsequent ALL therapy																			X	Collect if relapsed (yes, no). If relapsed was subsequent ALL therapy administered? If yes, what therapy?
[redacted]																				
[redacted]		[redacted]	[redacted]		[redacted]	[redacted]				[redacted]	[redacted]		[redacted]			[redacted]				[redacted]
PHARMACO-KINETIC ASSESSMENTS																				
Pharmacokinetic blood samples		X			X															Day 1: predose and within 2 min before EOI; day 8: predose, 15 min after the start of infusion, within 2 min before EOI; and 15, 60, and 120 min after EOI

ALL = acute lymphoblastic leukemia; ALP = alkaline phosphatase; ANC = absolute neutrophil count; anti-HBs = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; aPTT = activated partial thromboplastin time; BMA = bone marrow aspirate; CMV = cytomegalovirus; CNS = central nervous system; CR = complete remission; ECG = electrocardiogram; ECHO = echocardiogram; EOI = end of infusion; HBsAg = hepatitis B surface antigen; ICF = informed consent; INR = international normalized ratio; IT = intrathecal therapy; LTFU = long term follow-up; MRD = minimal residual disease; NGS = next generation sequencing; PCR = polymerase chain reaction; SFU = safety follow-up

[a] The safety follow-up visit is to be performed 30 days after the last dose of protocol specified systemic anti-leukemia therapy in induction or consolidation whichever is later, or prior to next therapy following induction if not proceeding to optional consolidation, or prior to next therapy after consolidation.

[b] After the safety follow-up visit, subjects are to continue follow-up every 12 weeks for up to 2 years.

[c] The timing of assessments on days 36 to 50 and when/if a subject proceeds to the consolidation phase is to be determined by the investigator based on the subject's peripheral blood count recovery or the start of alternate therapy, whichever comes first. Assessments may be repeated multiple times within this window at the discretion of the investigator as needed to assess for response or progression. If peripheral blood counts recover within 7 days of an M1 bone marrow assessment a repeat bone marrow is not required to confirm CR.

[d] Subjects with positive testing or a history of prior HBV infection should have consultation with a specialist and must have HBV-DNA testing at screening and again at safety follow-up. Subjects that have received hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV-DNA monitoring.

[e] Evaluations performed within 7 days of enrollment as part of routine medical care (eg, bone marrow aspirate/biopsy) may be used for screening assessments.

Table 17. Phase 2 Dose Regimen for Induction Therapy – Subjects Less Than 12 Months of Age at Screening

	Treatment Period (Induction Therapy Subjects Less Than 12 Months of Age)																Comments
Study Day	**1**	**2**	**3-7**	**8**	**9**	**10-11**	**12**	**13-14**	**15**	**16**	**17-21**	**22**	**23-27**	**28**	**29**	**36-50**	
STUDY TREATMENT																	
Carfilzomib	X	X		X	X				X	X							20 mg/m^2 on day 1, 56 mg/m^2 for subsequent doses. Administer IV over 30 $\pm$ 5 minutes
Prehydration	X	X		X	X				X	X							Greater than or equal to 125 mL/m^2/hour of IV fluid is required for 1 hour prior to carfilzomib administration
Vincristine				X					X			X			X		Less than 6 months of age: 1 mg/m^2 Greater than or equal to 6 months of age: 1.2 mg/m^2 Administer as IV push over 1 min or infusion per institutional policy. Dose should be rounded to nearest 0.01 mg and maximum single dose is 2 mg.
Prednisolone	X	X	X														Less than 6 months of age: 13 mg/m^2/dose TID (total daily dose = 39 mg/m^2) Greater than or equal to 6 months of age: 15 mg/m^2/dose TID (total daily dose = 45 mg/m^2) Oral, nasogastric, or IV administration On days 1 and 2, administered 4 hours to 30 minutes prior to carfilzomib. See Section 22.1.2.1 for acceptable alternatives.
Dexamethasone				X	X	X	X	X	X	X	X	X	X	X			Less than 6 months of age: 1.3 mg/m^2/dose TID (total daily dose = 3.9 mg/m^2) Greater than or equal to 6 months of age: 1.5 mg/m^2/dose TID (total daily dose = 4.5 mg/m^2) Oral, nasogastric, or IV administration. On days 8, 9, 15, and 16, administered 4 hour to 30 minutes prior to carfilzomib. Taper steroids to 0 mg over days 29 to 35. See Section 22.1.2.1 for acceptable alternatives.

	Treatment Period (Induction Therapy Subjects Less Than 12 Months of Age)																Comments
Study Day	**1**	**2**	**3-7**	**8**	**9**	**10-11**	**12**	**13-14**	**15**	**16**	**17-21**	**22**	**23-27**	**28**	**29**	**36-50**	
PEG-asparaginase							X										Less than 6 months of age: 1750 units/m^2 Greater than or equal to 6 months of age: 2000 units/m^2 Administer IV over 1 to 2 hours or IM. See Section 22.1.2.1 for acceptable alternatives.
Daunorubicin				X	X												Less than 6 months of age: 20 mg/m^2 Greater than or equal to 6 months of age: 23 mg/m^2 Administer as IV push or as an infusion over 1 to 15 minutes, or longer as per institutional practice. See Section 22.1.2.1 for acceptable alternatives.
IT methotrexate	X														X		6 mg. If a dose was received within 7 days of day 1 and was per protocol dosing, day 1 dose does not need to be repeated. Day 29 dose is administered with IT hydrocortisone.
IT cytarabine									X								15 mg, administer with hydrocortisone.
IT hydrocortisone									X						X		12 mg. See Section 22.1.4 for acceptable alternatives.

IM = intramuscular; IT = intrathecal; IV = intravenous; PEG = polyethylene glycol; TID = three times a day

Table 18. Phase 2 Schedule of Activities – Consolidation Therapy Subjects Greater Than or Equal to 12 Months of Age at Screening

	Treatment Period (Consolidation Therapy Subjects Greater Than or Equal to12 Months of Age)																		SFU[a]	LTFU (every 12 weeks)[b]	Comments
Study Day of Consolidation	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**18**	**22**	**29-45[c]**			
GENERAL AND SAFETY ASSESSMENTS																						
Physical examination	X																			X		
Vital signs	X							X							X			X	X	X		Temperature, heart rate, respiratory rate, and systolic and diastolic blood pressures. On days 29 to 45, assessment only required at time of bone marrow assessment.
Karnofsky or Lansky Performance status																				X		Lansky if less than 16 years of age; Karnofsky if greater than or equal to 16 years of age
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Collected from time of signing of the ICF. Details regarding the reporting of adverse events are provided in Section 24.2.4.
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Collected from time of signing of the ICF. Details regarding the reporting of serious adverse events are provided in Section 24.2.4.
Concomitant therapies review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Collected from time of signing of the ICF. Details regarding the reporting of concomitant therapies are provided in Section 22.7.2.
LABORATORY ASSESSMENTS																						

	Treatment Period (Consolidation Therapy Subjects Greater Than or Equal to12 Months of Age)																		SFU[a]	LTFU (every 12 weeks)[b]	Comments
Study Day of Consolidation	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**18**	**22**	**29-45[c]**			
Pregnancy test (females of childbearing potential only)	X																				Serum or urine. Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.
Hematology	X							X							X			X	X	X	See Table 28 for analytes. On days 29 to 45, assessment to be performed weekly, at the time of bone marrow assessment, and on day 45 in subjects that have not yet proceeded to next therapy, samples obtained on day of bone marrow and within 1 week after the bone marrow will be assessed locally and a stained slide must be sent to central lab, unless subject has already started next therapy.
Chemistry	X							X							X			X	X	X	See Table 28 for analytes. In addition to chemistries in the complete metabolic panel, include adjusted calcium, ALP, magnesium, phosphorous, serum albumin, and total protein if not part of standard panel; direct bilirubin if total bilirubin is elevated; and uric acid until normalized for 2 consecutive measurements. On days 29 to 45, assessment only required at time of bone marrow assessment.
Hepatitis B screening																				X	Only in subjects with positive hepatitis B serology at screening or past history of HBV infection. Testing performed locally.

	Treatment Period (Consolidation Therapy Subjects Greater Than or Equal to12 Months of Age)																		SFU[a]	LTFU (every 12 weeks)[b]	Comments
Study Day of Consolidation	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**18**	**22**	**29-45[c]**			
STUDY-SPECIFIC ASSESSMENTS																					
Bone marrow aspirate/biopsy																			X		On days 29 to 45, perform assessment when peripheral blood counts recover (defined as ANC greater than or equal to 1000/μL, platelets greater than or equal to 100 000/μL) or as clinically indicated, to assess for CR, by day 45, or as clinically indicated. MRD BMA using NGS has priority over MRD BMA flow cytometry or PCR. Bone marrow will be assessed locally and stained slides will be submitted to central laboratory for histological examination.
Lumbar puncture with or without IT	X							X							X			X	X			Lumbar puncture performed on days 15 and 22 only if CNS3 (Table 3). On days 29 to 45, assessment only required at time of bone marrow assessment.
Testicular ultrasound/physical exam (males with testicular mass only)																			X			Remission is to be determined by the same technique used at screening
Chest imaging (if mediastinal mass is present at screening only)																			X			On days 29 to 45, assessment only required at time of bone marrow assessment.
Other extramedullary disease assessment	X																			X		Only if clinically indicated, response should be assessed using same method used at screening
Vital Status																					X	

	Treatment Period (Consolidation Therapy Subjects Greater Than or Equal to12 Months of Age)																		SFU[a]	LTFU (every 12 weeks)[b]	Comments
Study Day of Consolidation	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**18**	**22**	**29-45[c]**			
Subsequent ALL therapy																				X	Collect if relapsed (yes, no). If relapsed was subsequent ALL therapy administered? If yes, what therapy?
[redacted]																					
[redacted]	[redacted]	[redacted]						[redacted]							[redacted]			[redacted]	[redacted]		[redacted]
PHARMACOKINETIC ASSESSMENTS																					
Pharmacokinetic blood samples	X																				Day 1: predose, 15 min after the start of infusion, within 2 min before EOI; and 15, 60, and 120 min after EOI

ALL = acute lymphoblastic leukemia; ALP = alkaline phosphatase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; BMA = bone marrow aspirate; CNS = central nervous system; CR = complete remission; ECG = electrocardiogram; ECHO = echocardiogram; EOI = end of infusion; ICF = informed consent; INR = international normalized ratio; IT = intrathecal therapy; LTFU = long term follow-up; MRD = minimal residual disease; NGS = next generation sequencing; PCR = polymerase chain reaction; SFU = safety follow-up

[a] The safety follow-up visit is to be performed 30 days after the last dose of protocol specified systemic anti-leukemia therapy in induction or consolidation whichever is later, or prior to next therapy following induction if not proceeding to optional consolidation, or prior to next therapy after consolidation

[b] After the safety follow-up visit, subjects are to continue follow-up every 12 weeks for up to 2 years.

[c] The timing of assessments on days 29 to 45 is to be determined by the investigator based on the subject's peripheral blood count recovery or the start of alternate therapy, whichever comes first. Assessments may be repeated multiple times within this window at the discretion of the investigator as needed to assess for response or progression. If peripheral blood counts recover within 7 days of an M1 bone marrow assessment a repeat bone marrow is not required to confirm CR.

Table 19. Phase 2 Dose Regimen for Consolidation Therapy – Subjects Greater Than or Equal to 12 Months of Age at Screening

	Treatment Period (Consolidation Therapy Subjects Greater Than or Equal to 12 Months of Age)																		Comments
Study Day of Consolidation	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**18**	**22**	**29-45**	
STUDY TREATMENT																				
Carfilzomib	X	X						X	X						X	X				56 mg/m^2 for all doses. Administer IV over 30 ± 5 minutes.
Prehydration and premedication	X	X						X	X						X	X				Greater than or equal to 125 mL/m^2/hour of IV fluid is required for 1 hour prior to carfilzomib administration. Oral, nasogastric, or IV administration of dexamethasone 3 mg/m^2 4 hours to 30 minutes prior to carfilzomib.
Cytarabine	X	X	X	X				X	X	X	X									75 mg/m^2 daily. Administer IV over 1 to 30 min or SC.
6-Mercaptopurine	X	X	X	X	X	X	X	X	X	X	X	X	X	X						60 mg/m^2 daily. Administer orally
Cyclophosphamide	X																			1 g/m^2 single dose. Administer IV over 30 to 60 min.
Vincristine															X			X		1.5 mg/m^2 per dose (maximum single dose 2 mg). Administer as IV push over 1 min or infusion per institutional policy.
PEG-asparaginase															X					1000 U/m^2 per dose. Administer IV over 1 to 2 hours. See Section 22.1.2.1 for acceptable alternatives.
IT – CNS negative at screening	X							X							X			X	day 29	Methotrexate dose is age dependent (see Figure 4.). IT therapy may be performed on day 29 per institutional standard practice. See Section 22.1.4 for acceptable alternatives.

	Treatment Period (Consolidation Therapy Subjects Greater Than or Equal to 12 Months of Age)																		Comments
Study Day of Consolidation	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**18**	**22**	**29-45**	
IT – CNS positive at screening	X							X							X			X	day 29	Methotrexate, cytarabine, and hydrocortisone doses are age dependent (see Figure 4). IT therapy may be performed on day 29 per institutional standard practice. See Section 22.1.4 for acceptable alternatives.

CNS = central nervous system; IT = intrathecal therapy; IV = intravenous; PEG = polyethylene glycol; SC = subcutaneous

Table 20. Phase 2 Schedule of Activities – Consolidation Therapy Subjects Less Than 12 Months of Age at Screening

	Treatment Period (Consolidation Therapy Subjects Less Than 12 Months of Age)																SFU[a]	LTFU (every 12 weeks)[b]	Comments
Study Day of Consolidation	**1**	**2**	**3-6**	**7**	**8**	**9**	**10**	**11-13**	**14**	**15**	**16**	**17-20**	**24**	**25-27**	**29**	**36-50[c]**			
GENERAL AND SAFETY ASSESSMENTS																			
Physical examination	X																X		
Vital signs	X				X					X			X			X	X		Temperature, heart rate, respiratory rate, and systolic and diastolic blood pressures. On days 36 to 50, assessment only required at time of bone marrow assessment.
Lansky Performance status																	X		Only if subject is greater than 12 months of age at start of consolidation
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Collected from time of signing of the ICF. Details regarding the reporting of adverse events are provided in Section 24.2.4.
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Collected from time of signing of the ICF. Details regarding the reporting of serious adverse events are provided in Section 24.2.4.
Concomitant therapies review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Collected from time of signing of the ICF. Details regarding the reporting of concomitant therapies are provided in Section 22.7.2.

	Treatment Period (Consolidation Therapy Subjects Less Than 12 Months of Age)																SFU[a]	LTFU (every 12 weeks)[b]	Comments
Study Day of Consolidation	**1**	**2**	**3-6**	**7**	**8**	**9**	**10**	**11-13**	**14**	**15**	**16**	**17-20**	**24**	**25-27**	**29**	**36-50[c]**			
LABORATORY ASSESSMENTS																			
Hematology	X				X					X		Day 17	X		X	X	X		See Table 28 for analytes. On days 36 to 50, assessment to be performed weekly starting on day 36, at the time of bone marrow assessment, and on day 50 in subjects that have not yet proceeded to next therapy, samples obtained on day of bone marrow and within 1 week after the bone marrow will be assessed locally and a stained slide must be sent to central lab, unless subject has already started next therapy.
Chemistry	X				X					X			X		X	X	X		See Table 28 for analytes. In addition to chemistries in the complete metabolic panel, include adjusted calcium, ALP, magnesium, phosphorous, serum albumin, and total protein if not part of standard panel; direct bilirubin if total bilirubin is elevated; and uric acid until normalized for 2 consecutive measurements. On days 36 to 50, assessment to be performed weekly starting on day 36 and at time of bone marrow assessment.
Hepatitis B screening																	X		Only in subjects with positive hepatitis B serology at screening or past history of HBV infection. Testing performed locally.

	Treatment Period (Consolidation Therapy Subjects Less Than 12 Months of Age)																SFU[a]	LTFU (every 12 weeks)[b]	Comments
Study Day of Consolidation	**1**	**2**	**3-6**	**7**	**8**	**9**	**10**	**11-13**	**14**	**15**	**16**	**17-20**	**24**	**25-27**	**29**	**36-50[c]**			
STUDY-SPECIFIC ASSESSMENTS																			
Bone marrow aspirate/biopsy																X			On days 36 to 50, perform assessment when peripheral blood counts recover (defined as ANC greater than or equal to 1000/μL and platelets greater than or equal to 100 000/μL) or as clinically indicated, to assess for CR, by day 50, or as clinically indicated. MRD BMA using NGS has priority over MRD BMA flow cytometry or PCR. Bone marrow will be assessed locally and stained slides will be submitted to central laboratory for histological examination.
Lumbar puncture with or without IT							X						X			X			On days 36 to 50, assessment only required at time of bone marrow assessment.
Testicular ultrasound/physical exam (males with testicular mass only)																X			Remission is to be determined by the same technique used at screening
Chest imaging (if mediastinal mass is present at screening only)																X			On days 36 to 50, assessment only required at time of bone marrow assessment.
Other extramedullary disease assessment	X																X		Only if clinically indicated, response should be assessed using same method used at screening
Vital status																		X	

	Treatment Period (Consolidation Therapy Subjects Less Than 12 Months of Age)																SFU[a]	LTFU (every 12 weeks)[b]	Comments
Study Day of Consolidation	**1**	**2**	**3-6**	**7**	**8**	**9**	**10**	**11-13**	**14**	**15**	**16**	**17-20**	**24**	**25-27**	**29**	**36-50[c]**			
Subsequent ALL therapy																		X	Collect if relapsed (yes, no). If relapsed was subsequent ALL therapy administered? If yes, what therapy?
[redacted]																			
[redacted]	[redacted]	[redacted]			[redacted]					[redacted]			[redacted]		[redacted]				[redacted]
PHARMACO-KINETIC ASSESSMENTS																			
Pharmacokinetic blood samples	X																		Day 1: predose, 15 min after the start of infusion, within 2 min before EOI; and 15, 60, and 120 min after EOI

ALL = acute lymphoblastic leukemia; ALP = alkaline phosphatase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; BMA = bone marrow aspirate; CNS = central nervous system; CR = complete remission; ECG = electrocardiogram; ECHO = echocardiogram; EOI = end of infusion; ICF = informed consent; INR = international normalized ratio; LTFU = long term follow-up; MRD = minimal residual disease; NGS = next generation sequencing; PCR = polymerase chain reaction; SFU = safety follow-up

[a] The safety follow-up visit is to be performed 30 days after the last dose of protocol specified systemic anti-leukemia therapy in induction or consolidation whichever is later, or prior to next therapy following induction if not proceeding to optional consolidation, or prior to next therapy after consolidation

[b] After the safety follow-up visit, subjects are to continue follow-up every 12 weeks for up to 2 years.

[c] The timing of assessments on days 30 to 50 is to be determined by the investigator based on the subject's peripheral blood count recovery or the start of alternate therapy, whichever comes first. Assessments may be repeated multiple times within this window at the discretion of the investigator as needed to assess for response or progression. If peripheral blood counts recover within 7 days of an M1 bone marrow assessment a repeat bone marrow is not required to confirm CR.

Table 21. Phase 2 Dose Regimen for Consolidation Therapy – Subjects Less Than 12 Months of Age at Screening

	Treatment Period (Consolidation Therapy Subjects Less Than 12 Months of Age)																Comments
Study Day of Consolidation	1	2	3-6	7	8	9	10	11-13	14	15	16	17-20	24	25-27	28[b]	36-50	
STUDY TREATMENT																	
Carfilzomib	X	X			X	X				X	X						56 mg/m^2 dose. Administer IV over 30 $\pm$ 5 minutes
Prehydration and premedication	X	X			X	X				X	X						Greater than or equal to 125 mL/m^2/hour of IV fluid is required for 1 hour prior to carfilzomib administration. Oral, nasogastric, or IV administration of dexamethasone 3 mg/m^2 4 hours to 30 minutes prior to carfilzomib.
Cytarabine[a]			X				X	X				X	X	X			Less than 6 months of age: 50 mg/m^2 Greater than or equal to 6 months of age: 56 mg/m^2 Administer as IV push or SC, daily on days 3-6, 10-13, 17-20, and 24-27. Subjects should have ANC greater than or equal to 300/μL and platelets greater than or equal to 30 000/μL to start each 4-day cytarabine block beginning on days 10, 17, and 24.
6-Mercaptopurine[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		$<$ 6 months of age: 40 mg/m^2 greater than or equal to 6 months of age: 45 mg/m^2 Administer orally, daily on days 1-28. Administer on an empty stomach. Actual dose per day should be varied, as needed, to yield a weekly dose as close to 280 mg/m^2 if less than 6 months, or 315 mg/m^2 if greater than or equal to 6 months, as possible.
Cyclophosphamide	X																Less than 6 months of age: 670 mg/m^2 greater than or equal to 6 months of age: 750 mg/m^2 Administer IV over 30 to 60 min.
Mesna	X																Less than 6 months of age: 134 mg/m^2/dose Greater than or equal to 6 months of age: 150 mg/m^2/dose Administer as IV over 15 minutes at 0, 4, and 8 hours from the start of cyclophosphamide
IT methotrexate													X				6 mg. Administer with hydrocortisone.

	Treatment Period (Consolidation Therapy Subjects Less Than 12 Months of Age)																Comments
Study Day of Consolidation	1	2	3-6	7	8	9	10	11-13	14	15	16	17-20	24	25-27	28[b]	36-50	
IT cytarabine							X										15 mg. Administer with hydrocortisone.
IT hydrocortisone							X						X				12 mg. See Section 22.1.4 for acceptable alternatives.

IT = intrathecal; IV = intravenous; SC = subcutaneous

[a] For infants requiring make up doses of cytarabine or mercaptopurine, the time window for post consolidation bone marrow should be adjusted to start 1 week after completion of all chemotherapy and end 3 weeks after completion of chemotherapy.

[b] Only applies to 6-Mercaptopurine, which is administered on days 1 to 28.

18. Phase 2: Introduction

18.1 Phase 2 Study Rationale

Approximately 20% of pediatric patients with T-cell ALL and 15% of patients with B-cell ALL will have a bone marrow relapse. Treatment outcomes for children with relapsed ALL are poor, with intensive therapy and HSCT, overall survival ranges from 20% to 40% for B-cell ALL and 0% to 25% for T-cell ALL using 1- to 10-year landmark analyses (Raetz and Teachey, 2016; Locatelli et al, 2012), and even lower in subjects with refractory or multiply relapsed ALL. Recent advances in therapy for relapsed B-cell ALL, including CD19 targeting immune therapies and CD22 antibody drug conjugates (ADC), have improved response rates in relapsed/refractory B-cell ALL (Bhojwani et al, 2019; Gore et al, 2018; Maude et al, 2018; Kantarjian et al, 2016). However, technical challenges for cell-based immunotherapies and relapse remain a significant problem. Many options are available for treatment of relapsed refractory ALL, but for patients with T-cell ALL or B-cell ALL that has relapsed after immune therapy, no treatment has been demonstrated to be preferred or effective and prognosis remains grim (Ruella and Maus, 2016). Effective treatment for patients who have failed conventional chemotherapy or newer immunotherapies requires tolerable regimens that induce deep durable responses that last long enough to permit subjects to undergo HSCT (Locatelli et al, 2012; Gaynon et al, 2005).

Cooperative groups have worked toward the identification of novel agents that can partner with chemotherapy regimens that can be tolerated in these extensively treated patients (Wayne et al, 2017). The COG AALL01P2 study was developed to provide a chemotherapy platform (VPLD) that was well tolerated in children with relapsed ALL for the purpose of combining with novel agents (Raetz et al, 2008, Wayne et al, 2017). The COG AALL07P1 trial combined the proteasome inhibitor bortezomib with VPLD and demonstrated promising efficacy, especially in subjects with relapsed T-cell ALL (Horton et al, 2019). The VXLD regimen in this study (Study 20140106) is similar to the VPLD regimen evaluated in the 01P2 and 07P1 studies by COG and uses the same chemotherapy agents evaluated in other VXLD-bortezomib trials (Messinger et al, 2012; Bertaina et al, 2017).

Carfilzomib has the potential to improve upon the results seen with bortezomib-VPLD or -VXLD chemotherapy combinations due to a more favorable safety profile with less off-target side effects, enhanced efficacy given the potential to be active in bortezomib-resistant tumor cells (Franke et al, 2012), increased sensitivity of ex vivo ALL

cells to carfilzomib over bortezomib (Niewerth et al, 2013), and the superiority of carfilzomib over bortezomib observed in a head-to-head phase 3 study in relapsed multiple myeloma (ENDEAVOR), (Dimopoulos et al, 2016).

The goal of this phase 2 part of the study is to investigate the clinical activity and safety of carfilzomib combined with VXLD (CFZ-VXLD) in pediatric subjects with relapsed and refractory ALL and to evaluate the effectiveness of the regimen as a means to bridge subjects to treatments with curative intent. An observational study (Study 20180065) is being conducted by Amgen in collaboration with the TACL consortium to collect a robust set of data in children with relapsed/refractory ALL. Subjects from this observational study that resemble the inclusion/exclusion criteria of the phase 2 part of the study will form an external control group that can be used to estimate the differences in CR rates of CFZ-VXLD versus standard of care regimens.

18.2 Background

18.2.1 Acute Lymphoblastic Leukemia

See Section 3.1 for background information on ALL.

18.2.2 Treatment Outcomes in Pediatric Relapsed ALL

Approximately 15% to 20% of pediatric patients with ALL will relapse. Patients with relapsed disease can be risk stratified and treated based on the risk of treatment failure. Length of first CR and site of relapse are the 2 most important prognostic factors for successful outcome after relapse (Chessells, 1998). With intensive therapy, that may include HSCT, overall survival after relapse ranges from 20% to 40% for B-cell ALL and 0% to 25% for T-cell ALL (from 1- to 10-year landmark analyses) (Raetz and Teachey, 2016; Locatelli et al, 2012). The goal of chemotherapy for relapsed ALL is to induce remission of sufficient depth and duration to allow the patient to receive potentially curative treatment with HSCT. Depending upon clinical characteristics at time of relapse, 25% to 80% of patients fail to achieve remission. Due to low quality remissions and toxicity of the salvage therapy, up to 50% of patients with relapsed ALL who do achieve a CR do not maintain the remission long enough to proceed to HSCT with currently available chemotherapy regimens (Gaynon et al, 2006; Gaynon, 2005).

The development of immune therapy (eg, blinatumomab, chimeric antigen receptor T cell therapy [CAR-T], or inotuzumab) in the last 8 years has improved remission rates in subjects with relapsed or refractory B-cell ALL and may improve long-term survival in at least a subset of children with relapsed ALL (Bhojwani et al, 2019; Gore et al, 2018;

Maude et al, 2018; Kantarjian et al, 2016). CAR-T therapy can induce CR in up to 90% of patients with B-cell ALL even in advanced (second or greater relapse) and refractory relapse (Maude et al, 2018). In addition, remissions induced with immune therapy are often very deep (MRD negative). However, within this population, there remains a substantial failure rate with immune therapies and outcomes for these patients are generally very poor (Ruella and Maus, 2016). In a clinical study of tisagenlecleucel, 66% of subjects achieved a CR, with 1-year relapse-free survival rates of 39% overall and 59% for responders (Maude et al, 2018). Similarly, the 1-year event-free survival rate for CAR-T therapy in advanced ALL is approximately 50% for treated patients and lower for blinatumomab (Gore et al, 2018; Maude et al, 2018). A subset of these patients might be bridged to HSCT with an effective reinduction chemotherapy regimen.

Most remissions for patients with relapsed T-cell ALL are short-lived suggesting high levels of residual disease and event-free survival is extremely poor ranging between 0% and 16% (from 1- to 10-year landmark analyses) (Tallen et al, 2010; Raetz et al, 2008; Gaynon et al, 2006; Giona et al, 1997). In contrast to the advances in relapsed B-cell ALL, CR rates and survival of children with relapsed T-cell ALL have shown no significant change for more than 20 years.

Despite the use of very intensive therapy in infants with ALL, long-term EFS is between 28% and 45% and markedly inferior to older children (Biondi et al, 2006; Chessells et al, 2002; Reaman et al, 1999; Silverman et al, 1997) due in part to a high incidence of mixed lineage leukemia rearrangements (Pieters et al, 2007). The EFS for infants decreases with age: 0% to 29%, 26% to 50%, and 49% to 71% for infants < 3, 3 to < 6, and > 6 months, respectively (Salzer et al, 2012). Attempts to intensify therapy in infants using a modification of VXLD therapy were associated with excessive induction toxicity (Salzer et al, 2012). Of the first 68 infants enrolled, 25% died, including 58% of infants < 90 days of age; median time to death was 21 days into induction (15 days for infants < 90 days old). Modifications to the dose regimen introduced in the Interfant-99 (Pieters et al, 2007) and later Interfant-06 study (Salzer et al, 2015) have decreased the incidence of induction deaths to nearly the same as older children. These modifications include additional supportive care recommendations regarding infection prevention (Salzer et al, 2015), a lower dose of daunorubicin, a pre-phase of prednisone (on days 1 to 7) followed by dexamethasone (on days 8 to 28), use of L-asparaginase, and inclusion of cytarabine during induction (Pieters et al, 2007). The proposed regimen for infants uses the COG AALL15P1 induction regimen, which was designed using the

amended Interfant-based AALL0631 induction regimen. One notable change in AALL0631 was the substitution of L-asparaginase with pegaspargase, contributing to a lower cumulative dose. This de-intensification, along with additional supportive care recommendations, increased complete remission rates and decreased induction deaths (Salzer et al, 2015). Although the AALL15P1 study is for newly diagnosed ALL subjects, there are no published pediatric cooperative group studies for infants with relapsed ALL to reference for Study 20140106.

18.2.2.1 Rationale for Incorporating Proteasome Inhibitor with VXLD

Several pediatric studies combining the first-generation proteasome inhibitor, bortezomib, with VXLD have demonstrated that the safety profile for the combination is similar to that of VXLD alone with the same bortezomib dose/schedule as that used in adults with multiple myeloma (Bertaina et al, 2017; Horton et al, 2013; Messinger et al, 2012; Messinger et al, 2010). The combination of bortezomib and VXLD/VPLD demonstrated very promising rates of CR and MRD response in several difficult-to-treat patient populations, including very early relapse, relapse after blinatumomab or stem cell transplant, or multiple relapses.

Carfilzomib has the potential to improve upon the results seen with bortezomib plus chemotherapy combinations due to a more favorable safety profile with less off-target side effects, enhanced efficacy given the potential to be active in bortezomib-resistant tumor cells (Franke et al, 2012), increased sensitivity of ex vivo ALL cells to carfilzomib over bortezomib (Niewerth et al, 2013), and the superiority of carfilzomib over bortezomib observed in a head-to-head phase 3 study in relapsed multiple myeloma (ENDEAVOR), with significantly less neuropathy (Dimopoulos et al, 2017; Dimopoulos et al, 2016).

18.2.3 Therapeutic Needs in Relapsed or Refractory ALL

Because outcomes remain poor for patients with relapsed or refractory T-cell ALL and relapsed or refractory B-cell ALL who have relapsed after targeted immune therapy, these patients represent a significant unmet need. Thus, there is a clear need for novel agents to improve outcomes for these patients.

Based on the efficacy observed with bortezomib therapies, carfilzomib in combination with conventional chemotherapy is expected to play an important role for addressing this unmet need. While carfilzomib plus VXLD is not expected to be a curative therapy, carfilzomib offers the potential to increase the incidence and depth of remissions compared with existing therapies with acceptable safety, thereby acting as a bridge to

HSCT or other curative therapies in children and adolescents with relapsed or refractory ALL.

In the phase 1b portion of Study 20140106, carfilzomib in combination with VXLD **showed** promising efficacy, with CR rates of 43% after induction and 55% overall in this population of pediatric patients with relapsed or refractory B- or T-cell ALL. The phase 2 part of this study will further evaluate the efficacy and safety of carfilzomib in combination with VXLD as a treatment in children with an otherwise dismal prognosis.

18.2.4 Justification of Treatment Effect

After relapse the probability of achieving remission with salvage therapy varies based on several known risk factors including site of relapse, duration of first remission, number of relapses, and immune phenotype (T- vs B-cell) (Raetz and Bhatla, 2012). In addition, subjects that are refractory to one or more salvage attempts have a markedly reduced chance of responding to subsequent salvage attempts. Most studies of relapsed B- or T-cell ALL have tested salvage treatments in the setting of first untested (non-refractory) relapse. In addition, because the usual endpoint in relapse studies is full CR, subjects that have received HSCT have typically been excluded due to reduced capacity for bone marrow recovery and greater toxicity observed in these subjects. For example, the COG AALL01P2 study evaluated the VPLD and UKALLR3 trial the R3 regimens respectively, both studies limited enrollment to first untreated relapse and excluded subjects that had received prior HSCT (Raetz et al, 2008, Parker et al, 2010). Approximately 50% of subjects enrolled on the UKALLR3 study had late bone marrow relapse and another 22% isolated extramedullary relapse. These patient populations have a much higher probability of responding to therapy than subjects enrolling in the current study.

To establish a treatment effect for the VXLD-carfilzomib regimen it was hypothesized that the characteristics important for prediction of CR response enrolling in the phase 2 can be predicted from the characteristics of the subjects that have enrolled in the phase 1 portion of the study. The characteristics evaluated included number of relapses, refractory relapse, prior HSCT, duration of first remission, and immune phenotype. The actual remission rate in the phase 1 portion of the study was then compared to the remission rate expected for subjects with these same characteristics. Although only a fraction of subjects with B-cell ALL that enrolled in phase 1 had relapsed after receiving immune therapy, it was anticipated that the observed differences in remission rates based on the evaluated characteristics would be similar.

A summary of the proportion of subjects stratified by immune phenotype, number of relapses, refractory relapses, early and very early first relapse, and prior HSCT is shown in Table 22. The patient characteristics enroll**ed** in Amgen's **now closed** phase 1 study and anticipated to reflect the characteristics of subjects enrolling in the proposed phase 2 part of the study, have a much higher risk of treatment failure compared to the COG AALL02P1 or UKALL-R3 study. The more restrictive eligibility requirements for subjects with relapsed B-cell ALL will further reduce the comparability of the CR rates of the phase 2 population from that of either of these studies.

Table 22. Covariate Distribution for Phase 1 Subjects

Subject Covariates N = 22	1st very early relapse	1st early relapse	1st refractory relapse	1st relapse Prior HSCT	1st refractory relapse prior HSCT	2nd relapse	2nd refractory relapse	2nd relapse Prior HSCT	2nd refractory relapse Prior HSCT	3rd relapse
T cell n = 10	2[a]	2	1(3)[a]	1	3 [a,a,a]	1 [a]				
B cell (>1st relapse) n = 6	--	--	--	--	--	1 [a]	2(4[b,c],1)	1	1[d]	1[b]
B cell 1st relapse n = 6	4[a]	1[a]		1[a (d)]						

Data as of 07 June 2020
Very early relapse = first remission duration <18 months, early relapse = first remission 18-36 months, HSCT = hematopoietic stem cell transplant
( ) number indicates number of refractory salvage regimens prior to study enrollment
[a] 1 subject in each cell for each [a] had primary induction failure
[b] Relapse after CAR-T
[c] Relapse after blinatumomab
[d] Relapse after inotuzumab, (d) Inotuzumab for primary induction failure

Trial data to estimate the probability of CR for subjects with these covariates were obtained from several data sources. For subjects with T-cell ALL in first untreated relapse who did not previously receive a prior HSCT the CR rate after treatment with VPLD have been reported for the COG AALL02P1 study. The regimen used in that study replaced dexamethasone with an equivalent dose of prednisone but was otherwise similar to the VXLD regimen for Study 20140106. The CR rate was 29%, 2 of 7 subjects with T-cell achieved a full CR (Raetz, et al, 2008). The CR rate for subjects with B-cell ALL who had a first untreated bone marrow relapse and received VXLD salvage therapy, was reported from 539 subjects who relapsed after being treated on the 1900 frontline series of COG studies (1997 to 2002). The CR rate for VXLD was 38% and 80% for subjects with a first remission less than 18 months and 18 to 36 months, respectively (Harned and Gaynon, 2008). The CR rate for subjects with multiple and/or refractory relapse were derived from a TACL study that evaluated all salvage attempts with intent to induce remission at 8 large academic centers over a 10-year time period (Ko et al, 2010). A second retrospective study was performed but did not include outcomes for patients with T-cell ALL (Sun et al, 2018). Among 98 salvage procedures the CR rate for first, second, or greater than second refractory relapse were 20%, 24%, and 6% respectively, and among 116 salvage attempts for untested second and third relapse were 48% (45 of 93) and 30% (7 of 23) respectively. In the TACL study, subjects with B-cell ALL represented 87% of the patient population and T-cell 13%. The odds ratio for reinduction failure among subjects with relapsed T versus B-cell ALL was 2.0 (Ko et al, 2010). CR probabilities for T-cell subjects with refractory or multiple relapses were estimated by reducing the CR rate reported for the overall population by an odds ratio for failure of 2.0. The CR estimates obtained from the TACL study represent approximations because the salvage regimens were not defined (only that they were considered to be intended to induce remission), the definition of CR required a lower neutrophil and platelet recovery than standard definition of CR, and CR without platelet recovery was included in the definition of CR. These limitations are likely to have inflated the salvage CR rates; however, it is not possible to fully account for the impact of these variables on the CR estimates.

To assess the potential impact of a prior HSCT on the probability of achieving CR following relapse, an Amgen external control database that was provided to FDA as part of the blinatumomab request for marketing authorization was evaluated (Study 20140228). This real-world data set included 144 subjects from the European Union and 83 subjects from the United States. The probability of achieving CR for

subjects who received a prior HSCT was 38.6% (58 of 150) and for those relapsing without a prior HSCT, it was 50.6% (39 of 77), an odds ratio of 1.63 favoring re-induction failure in subjects with a prior HSCT. CR rates for subjects who relapsed after HSCT were first adjusted for other characteristics and then further decreased using an odds ratio of 1.63. The final weighted CR rate based on the characteristics listed in Table 22. and methods of adjustments described yielded a CR rate for the control population of approximately 15% for T cell and 25% for B-cell. Based on proposed mitigation procedures in the phase 2 part of the study that will allow for peripheral blood count recovery prior to bone marrow assessment the CR rate predicted from the phase 1 part of the study is 60% for B-cell ALL and 30% for T-cell ALL.

18.2.5 Amgen Investigational Product Background: Carfilzomib

Carfilzomib (formerly known as PR-171) is a tetrapeptide epoxyketone based inhibitor of the chymotrypsin like activity of the 20S proteasome. The preclinical background for carfilzomib is summarized in Section 3.2.1, and the clinical background for carfilzomib is summarized in Section 3.2.2.

A detailed description of the chemistry, pharmacology, efficacy, and safety of carfilzomib is provided in the Carfilzomib Investigator's Brochure.

18.2.6 Non-investigational Product Background: VXLD, Modified BFM, and Intrathecal Chemotherapy

Refer to the regional manufacturer package inserts for additional information.

18.3 Benefit/Risk Assessment

The following benefit-risk assessment supports the conduct of this clinical study.

Reference should be made to the Carfilzomib Investigator's Brochure for further data on carfilzomib.

18.3.1 Therapeutic Context

Outcomes for patients with relapsed or refractory ALL remain poor for subjects with T-cell ALL and those with B-cell ALL that have relapsed after targeted immune therapy, therefore these subjects represent a significant unmet need. Thus, there is a clear need for novel agents to improve outcomes for these patients.

18.3.2 Key Benefits

For patients with relapsed ALL, the first step toward cure is the achievement of complete remission. As previously reviewed in Section 18.2.2.1, several studies in pediatric patients with relapsed/refractory ALL demonstrated promising efficacy when combining

bortezomib with VXLD (Bertaina et al, 2017; Horton et al, 2013; Messinger et al, 2012; Messinger et al, 2010). In a recent update of COG AALL07P1 study (VPLD + bortezomib) outcomes, the CR rate for subjects with T-cell disease was 68% (15/22 subjects) (Horton et al, 2019) compared to 29% (2/7) in subjects with relapsed T-cell ALL treated in COG AALL01P2 (VPLD) (Raetz et al, 2018). For children with relapsed B-cell ALL, a direct comparison of the CR rates in subjects with very early relapse between AALL07P1 (VPLD-bortezomib) and AALL01P2 (VPLD) was 63% (29/46) vs 56% (9/16). In a much larger series, a CR rate of 38% was reported among children with very early first relapse treated with a single cycle of VXLD (Harned and Gaynon, 2008). These results support the use of proteasome inhibition in the treatment of relapsed pediatric ALL. As previously reviewed in Section 18.2.2.1, nonclinical data with ALL blast cells and clinical data in relapsed multiple myeloma indicate that carfilzomib is a more effective proteasome inhibitor than bortezomib. As reviewed in Section 18.2.4, the results of VXLD-carfilzomib from the **now closed** phase 1 part of the study predict an approximate doubling of the CR rate, after accounting for covariates predictive for the probability of CR, 15 vs 30% for T-cell ALL and 25 vs 60% for multiply relapsed B-cell ALL.

The potential benefits of the carfilzomib-VXLD regimen include improved disease response with an improved chance of achieving a remission that is deep and durable enough to permit subjects to undergo hematopoietic stem cell transplant or other potential curative treatments. An improved CR rate and increased number of MRD negative responses may translate into a better chance for disease free and overall survival.

18.3.3 Key Risks

The characterization of the risks associated with carfilzomib is based on clinical trial data evaluating the use of carfilzomib in combination with other drugs for the treatment of adult subjects with relapse/refractory multiple myeloma as well as post marketing experience in adult patients. Thus, the incidence and nature of risks associated with carfilzomib may be different in the population of pediatric subjects with ALL in this study.

For the phase 1 part of the 20140106 study, as of the cutoff date of 23 July 2020, a total of 22 subjects have been treated in the VXLD induction arm. Out of 17 DLT-evaluable subjects, 1 DLT (grade 4 pulmonary hemorrhage) was observed at a dose 20 mg/m^2. All grade treatment-emergent adverse events reported in the induction phase with > 30% incidence included events with the following PTs: hypertension (40.9%), platelet

count decreased (36.4%), anaemia (31.8%), and pyrexia (31.8%). Serious adverse events with 2 or more events included events with the following PTs: bacillus bacteraemia (n = 2), posterior reversible encephalopathy syndrome (n = 2), and pancreatitis acute (n = 2). The pancreatitis acute events were considered most likely associated with PEG-asparaginase. The PTs for fatal treatment-emergent adverse events were: acute lymphocytic leukaemia (n = 1, in the setting of multiorganism sepsis) and pneumonia (n = 1), both at the 56 mg/m^2 dose.

In the consolidation phase, a total of 11 subjects were treated. The PTs for the all grade treatment-emergent adverse events with > 30% incidence in the consolidation phase were: anaemia (72.7%), nausea (63.6%), febrile neutropenia (54.5%), hypertension (54.5%), platelet count decreased (54.5%), alanine aminotransferase increased (45.5%), abdominal pain (36.4%), aspartate aminotransferase increased (36.4%), headache (36.4%), hypoalbuminaemia (36.4%), hypokalaemia (36.4%), pyrexia (36.4%), and vomiting (36.4%). The PTs for the serious adverse events with 2 or more events included: febrile neutropenia (n = 6), drug hypersensitivity (n = 2) and posterior reversible encephalopathy syndrome (n = 2). There were no fatal treatment-emergent adverse events reported.

18.3.3.1 Cardiac Toxicity

New onset or worsening of pre-existing cardiac failure (eg, congestive heart failure, pulmonary edema, decreased ejection fraction), including fatalities, have occurred after administration of carfilzomib. In clinical studies with carfilzomib, these events occurred throughout the course of carfilzomib therapy.

ASPIRE evaluated carfilzomib at a dose of 27 mg/m^2 twice weekly in combination with lenalidomide and dexamethasone (KRd) versus lenalidomide and dexamethasone (Rd) in adult subjects with relapsed or refractory multiple myeloma. Incidence of cardiac failure events reported in ASPIRE was as follows: all grades: KRd: 7.1%, Rd: 4.1%; serious adverse events: KRd: 4.1%, Rd: 2.1%; grade ≥ 3 adverse events: KRd: 4.3%, Rd: 2.1%. Most of the cardiac failure adverse events (all grades) were resolved (KRd: 3.3%, Rd: 1.5%) or stabilized/not resolving (KRd: 2.6%, Rd: 1.5%) or resolved with sequelae (KRd: 0.5%, Rd: 0%). Fatal outcomes were reported for 0.8% subjects from the KRd group and 1.0% from the Rd group. Cardiac failure adverse events (all grades) leading to discontinuation of any investigational product were reported for 0.5% of subjects from the KRd group and 0.8% of subjects from the Rd group.

ENDEAVOR evaluated carfilzomib and low-dose dexamethasone (Kd) versus bortezomib plus low-dose dexamethasone (Vd) in adult subjects with relapsed or refractory multiple myeloma. Incidence of cardiac failure events reported in ENDEAVOR was as follows: all grades: Kd: 10.8%, Vd: 3.3%; serious adverse events: Kd: 3.9%, Vd: 1.3%; grade ≥ 3 adverse events: Kd: 5.8%, Vd: 2.0%. Most of the cardiac failure adverse events (all grades) were resolved (Kd: 3.7%, Vd: 2.0%) or stabilized/not resolving (Kd: 6.7%, Vd: 0.9%). Fatal outcomes were reported for 0.2% subjects from the Kd group and 0.4% from the Vd group. Cardiac failure adverse events (all grades) leading to discontinuation of any investigational product were reported for 3.7% of subjects from the Kd group and 0.9% of subjects from the Vd group.

Subjects with New York Heart Association Class III and IV heart failure, recent myocardial infarction, and conduction abnormalities uncontrolled by medications were not eligible for the clinical study and may be at greater risk for cardiac complications.

18.3.3.2 Hypertension

Hypertension has been reported as one of the common comorbidities in patients with multiple myeloma. Based on the MarketScan claims database, the prevalence of hypertension as a comorbidity among multiple myeloma patients is 46.9% (Song et al, 2016) and there was a 30% increase in the risk of hypertension in multiple myeloma versus non-multiple myeloma patients (Chari et al, 2016). The incidence of hypertension adverse events in ASPIRE was as follows: all grades: KRd: 17.1%, Rd: 8.7%, serious adverse events: KRd: 0%, Rd: 0.3%; grade ≥ 3 adverse events: KRd: 6.4%, Rd: 2.3%. The incidence of hypertension (all grades) was higher in subjects with a history of hypertension: with history of hypertension: KRd: 20.5%, Rd: 10.7%; without history of hypertension: KRd: 13.7%, Rd: 7.1%. No fatal outcomes for hypertension adverse events (all grades) were reported in ASPIRE. Almost all the hypertension adverse events (all grades) were stabilized/not resolving (KRd: 8.7%; Rd: 4.4%) or resolved (KRd: 8.4%, Rd: 4.1%); resolved with sequelae was also reported (KRd: 0%, Rd: 0.3%). Hypertension adverse events (all grades) led to discontinuation of any investigational product in 0.3% subjects from the KRd and Rd groups each. Hypertensive crisis occurred in ≤ 0.5% of subjects (KRd: 0.5%, Rd: 0.3%); all these adverse events were ≥ grade 3.

The incidence of hypertension adverse events in ENDEAVOR was as follows: all grades: Kd: 33.7%, Vd: 10.5%, serious adverse events: Kd: 0.9%, Vd: 0.2%; grade ≥ 3

adverse events: Kd: 15.6%, Vd: 3.3%. The incidence of hypertension (all grades) was similar in subjects with a history of hypertension and subjects without a history of hypertension: subjects with history of hypertension: Kd: 31.1%, Vd: 10.8%; subjects without history of hypertension: Kd: 36.4%, Vd: 10.3%. No fatal outcomes for hypertension adverse events (all grades) were reported in ENDEAVOR. The outcomes for hypertension adverse events reported in ENDEAVOR were stabilized/not resolving (Kd: 19.4%, Vd: 4.2%) and resolved (Kd: 14.0%, Vd: 6.1%). Hypertension adverse events (all grades) led to discontinuation of any investigational product in 0.2% subjects from the Kd group and 0% of subjects from the Vd group. Hypertensive crisis occurred in 0.2% of subjects in the Kd group and 0% of subjects in the Vd group, all of these adverse events were ≥ grade 3.

Blood pressure is monitored while on study and hypertension should be treated as needed. If hypertension cannot be controlled, the carfilzomib dose should be held. In case of hypertensive crisis, carfilzomib should be stopped until the hypertensive crisis resolved. The investigator may consider restarting carfilzomib based on an individual benefit-risk assessment.

18.3.3.3 Acute Renal Failure

Renal failure is a relatively common problem in patients with multiple myeloma (Dimopoulos et al, 2016; Bladé and Rosiñol, 2005). Acute renal failure occurs most often in patients with multiple myeloma who have high rates of production and excretion of immunoglobulin (Ig)-free light chains, which may be toxic to the basement membranes of the glomeruli and/or the renal tubules and form obstructing tubular casts, particularly if the patient is dehydrated (Dimopoulos et al, 2016; Sanders and Booker, 1992).

The incidence of acute renal failure in ASPIRE was as follows: all grades: KRd: 9.2%, Rd: 7.7%; serious adverse events: KRd: 2.6%, Rd: 1.8%; grade ≥ 3 adverse events: KRd: 3.8%, Rd: 3.3%. Most of the acute renal failure adverse events (all grades) were resolved (KRd: 6.1%, Rd: 5.7%) or stabilized/not resolving (KRd: 2.8%, Rd: 1.8%) or resolved with sequelae (KRd: 0.3%, Rd: 0%). No fatal outcomes were reported for the KRd group; in the Rd group, fatal outcomes were reported for 0.3% of the subjects. Acute renal failure adverse events (all grades) leading to discontinuation of any investigational product were reported for 0.5% of subjects in the KRd group and 1.0% in the Rd group.

The incidence of acute renal failure in ENDEAVOR was as follows: all grades: Kd: 10.4%, Vd: 6.1%; serious adverse events: Kd: 3.9%, Vd: 2.0%; grade ≥ 3 adverse events: Kd: 5.6%, Vd: 3.3%. Most of the acute renal failure adverse events (all grades) were resolved (Kd: 5.6%, Vd: 3.1%) or stabilized/not resolving (Kd: 4.5%, Vd: 3.1%). Fatal outcomes were reported for 0.2% of the subjects in the Kd group, in the Vd group no fatal outcomes were reported. Acute renal failure adverse events (all grades) leading to discontinuation of any investigational product were reported for 1.3% of subjects in the Kd group and 0.4% in the Vd group.

Acute renal failure was reported more frequently in patients with advanced relapsed or refractory multiple myeloma who received carfilzomib monotherapy. The incidence was increased in patients with a decrease in estimated creatinine clearance, calculated using Cockcroft and Gault equation, prior to receiving carfilzomib. Renal function should be monitored with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or stop dose as described in the dose modification (Section 22.2).

19. Phase 2: Objectives and Endpoints

All primary and secondary objectives will be analyzed for T-cell and B-cell ALL analysis sets separately, unless otherwise specified. For definitions of CR, CRp, CRh, CRi, SD and PD see Table 26. For the primary and secondary endpoint evaluation, response will be derived by the sponsor based upon local evaluation of bone marrow, peripheral blood, and extramedullary disease status. Minimal residual disease status will be determined per central lab review of bone marrow MRD using NGS.

Objectives	Endpoints
Primary	
• Compare the rate of CR of CFZ-VXLD at the end of induction therapy to an appropriate external control.	• CR after induction therapy
Primary Endpoint Estimand	
The OR for the PoCR for CFZ-VXLD versus external control.	
Secondary	
• Evaluate the safety and tolerability of CFZ-VXLD	• Treatment-emergent and treatment-related adverse events and severe adverse events and laboratory abnormalities during the induction therapy and consolidation therapy
• Compare the rate of CR, CRp, CRh, and CRi of CFZ-VXLD at the end of induction therapy relative to an appropriate external control	• CR, CRp, CRh, and CRi at the end of induction therapy

• Compare EFS for CFZ-VXLD to an appropriate external control	• EFS, defined as time from initiation of therapy until treatment failure (defined as failure to reach at least a CRi after consolidation or after induction in subjects that do not receive consolidation), relapse, or death from any cause
• Compare OS for CFZ-VXLD relative to an appropriate external control	• OS defined as time from initiation of therapy until death from any cause
• Estimate the DOR for CFZ-VXLD relative to an appropriate external control	• DOR, defined as time from earliest of CR, CRp, CRh, or CRi to relapse or death from any cause
• Estimate the rate of MRD[-] at the end of induction in subjects receiving CFZ-VXLD	• MRD status using NGS less than 10^{-4} after induction therapy in subjects achieving CR
• Estimate the rate of MRD[-] bone marrow after induction and consolidation therapy in subjects with B-cell ALL **or T-cell ALL** receiving CFZ-VXLD	• MRD status using NGS less than 10^{-3} and less than 10^{-4} in subjects achieving CR, CRp, CRh, or CRi after induction and consolidation therapy**, separately**
• Estimate the proportion of subjects that bridge to stem cell transplant or CAR-T cell therapy in subjects receiving CFZ-VXLD	• Occurrence of a stem cell transplant or CAR-T, without an intervening relapse after protocol specified therapy
• Estimate the rate of CR, CRp, CRh, and CRi of CFZ-VXLD at the end of consolidation therapy in subjects receiving CFZ-VXLD.	• CR, CRp, CRh, and CRi after consolidation
• Estimate the pharmacokinetics of carfilzomib when administered as part of VXLD regimen	• Carfilzomib pharmacokinetic parameters, including AUC, C_{max}, and if feasible, $t_{1/2}$

[redacted]

AUC = area under the concentration-time curve; CAR-T = chimeric antigen receptor T cell therapy; CFZ = carfilzomib; C_{max} = maximum plasma concentration; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; CRp = complete remission with incomplete recovery of platelets; DOR = duration of response; EFS = event-free survival; MRD = minimal residual disease; MRD[-] = minimal residual disease negative bone marrow; NGS = next generation sequencing; OS = overall survival; $t_{1/2}$ = half-life; VXLD = vincristine, dexamethasone, PEG asparaginase, daunorubicin

20. Phase 2: Study Design

20.1 Overall Design

The phase 2 portion of the study is a multicenter, single-group, externally-controlled study of carfilzomib in combination with VXLD in a minimum of 100 subjects, unless futility is met. Eligible subjects must be greater than or equal to 1 month to less than 21 years old, with their original diagnosis at less than 18 years of age and must have ALL with bone marrow relapse (greater than or equal to 5% leukemia blasts in bone marrow) or refractory relapse with or without extramedullary disease of the T-cell phenotype or of the B-cell phenotype after having received a targeted B-cell immune therapy (eg, blinatumomab, inotuzumab, CAR-T, or therapy). Infants enrolling on this study will receive a modified VXLD and optional consolidation based on the dose and schedule used in COG AALL15P1 study.

The carfilzomib dose for phase 2 will be 20 mg/m^2 on day 1 of induction, 56 mg/m^2 on days 2, 8, 9, 15, and 16 of induction and days 1, 2, 8, 9, 15, and 16 of consolidation.

Eligible subjects will be treated with VXLD plus carfilzomib for 1 cycle (induction), followed by assessment of treatment response. All subjects who do not show progression during induction will undergo a bone marrow and extramedullary disease evaluation after completion of induction therapy between days 29 to 45 of induction (between days 36 to 50 for infants), based on blood count recovery but before the start of post-induction therapy, whichever comes first. Response will be assessed per local and central laboratory review of bone marrow, peripheral blood and differential, and local assessment for sites of extramedullary disease. Minimal residual disease will be assessed by NGS central laboratory review and local evaluation by flow cytometry and/or PCR or NGS when available.

Subjects without disease progression as defined in Table 26 after induction may, at the investigator's discretion, be treated with 1 cycle of consolidation chemotherapy plus carfilzomib. Subjects who do not show disease progression during consolidation will be assessed for treatment response between day 29 to 45 of consolidation (between

day 36 to 50 for infants), based on blood count recovery or start of alternative therapy, whichever comes first.

Treatment response after consolidation therapy will also be assessed per local and central laboratory review of bone marrow, peripheral blood and differential, and local assessment for sites of extramedullary disease. When available, local laboratory assessments of MRD by flow cytometry and/or PCR or NGS will be collected. The consolidation treatment will consist of one 28-day cycle of Children's Oncology group-modified Berlin-Frankfurt-Munster (BFM) therapy; cyclophosphamide, cytarabine, 6-mercaptopurine, PEG-asparaginase, vincristine, and IT therapy, or for < 12 months of age a modified infant consolidation from COG AALL15P1; cyclophosphamide, cytarabine, 6-mercaptopurine, and IT therapy, combined with carfilzomib at a dose of 56 mg/m^2 (or lower if dose reduction was required during induction) at the same schedule as the induction therapy. After completion of study therapy, subjects will be followed for subsequent treatment(s), event-free and overall survival.

For selected objectives, the treatment response to induction of subjects receiving CFZ-VXLD will be compared to an external control arm of subjects from an observational study of relapsed pediatric ALL (**S**tudy 20180065) that received standard-of-care (SoC) chemotherapy, after appropriate adjustment. More details will be included in the statistical analysis plan.
The phase 2 part of the study design is described by a study schema in Section 17.11.1. The endpoints are defined in Section 19.

20.2 Number of Subjects

A minimum of 100 subjects will be enrolled and receive at least one dose of carfilzomib in the phase 2 part of the study unless futility is met. A minimum of 30 subjects with T-cell ALL and 50 subjects with B-cell ALL will be enrolled.

Subjects in this clinical investigation shall be referred to as "subjects". For the sample size justification, see Section 25.2.

20.2.1 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

20.3 Justification for Investigational Product Dose

Carfilzomib has been evaluated as a single agent and as part of a combination regimen for the treatment of adult subjects with multiple myeloma. The MTD for single agent carfilzomib administered by IV infusion over 30 minutes on 2 consecutive days per week has been determined to be 56 mg/m^2 (Study PX-171-007; data on file). In combination

with melphalan and prednisone, the MTD of carfilzomib administered on this same schedule has been determined to be 36 mg/m^2 in adults with relapsed or refractory multiple myeloma (Kolb et al, 2012). Current practice is to start with 20 mg/m^2 of carfilzomib before escalating to a higher dose.

Carfilzomib was investigated in the phase 1b portion of this study administered alone and in combination with induction chemotherapy, for the treatment of relapsed or refractory ALL. The recommended phase 2 dose, 56 mg/m^2, was selected for combination with VXLD by the Cohort Safety Review Committee (CSRC) based on review of safety, efficacy, pharmacokinetic, and [redacted] data obtained from the phase 1b portion of the study described above.

The selected dosing regimen of carfilzomib for the phase 2 portion of the study will consist of twice-weekly IV infusions (30 $\pm$ 5 minutes) on days 1, 2, 8, 9, 15 and 16 of the induction cycle. Subjects will receive 20 mg/m^2 carfilzomib on day 1 of the induction cycle, and 56 mg/m^2 on dosing days thereafter.

Based on preliminary pharmacokinetic analyses in 14 pediatric subjects, carfilzomib exposure was approximately dose proportional between the dose range of 27 to 56 mg/m^2, when given in combination with the VXLD backbone. Furthermore, dose-normalized exposures (C_{max} and AUC) in subjects $<$ 6 years, between 6 to 12 years, and $>$ 12 years of age were similar, suggesting little to no impact of age on carfilzomib pharmacokinetics in this population. When compared to the adult multiple myeloma population (dose range 20 to 56 mg/m^2), the geometric mean of dose-normalized exposures was similar; pharmacokinetic variability in pediatric subjects was high (%CV $\geq$ 49%), consistent with the observed variability in adult multiple myeloma subjects.

Preliminary pharmacokinetic/pharmacodynamic analyses did not reveal any clear dose- or exposure-dependent relationships for efficacy. Carfilzomib pharmacodynamics, as assessed by inhibition of proteasome activity (ie, chymotrypsin-like activity) in whole blood, were inhibited by over 90% following IV administration of 36 mg/m^2 and higher, although proteasome activity of other subunits (ie, caspase-like and trypsin-like activity) were not maximally suppressed. No clear trends in carfilzomib exposure were observed between responders and non-responders.

Based on the observed efficacy in adult multiple myeloma subjects, similar dose-normalized exposures in children and adults, and observed pharmacodynamics,

these data suggest 36 to 56 mg/m^2 may be an appropriate phase 2 dose, provided an acceptable safety and tolerability profile as determined by the CSRC.

20.3.1 Justification for Non-investigational Product Dose

For induction, VXLD products are to be administered in accordance with the terms of marketing authorizations.

For consolidation, if applicable, modified BFM products are to be administered in accordance with the terms of marketing authorizations.

20.4 End of Study

The end of study date is defined as the date when the last surviving subject completes the safety follow-up, discontinues the study due to death, is lost to follow-up, withdraws full consent from the study, or the sponsor in consultation with regulatory authorities decides to close the study, whichever occurs first.

The duration of the trial for an individual subject is estimated to be up to approximately 29 months (including the screening, safety follow-up [30 days], and long-term follow-up [up to 2 years after safety follow-up]).

21. Phase 2: Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive Response Technology (IRT).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 24.1.1).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

21.1 Inclusion Criteria

Subjects are eligible to be included in the phase 2 part of the study only if all of the following criteria apply:

110 Subject's legally acceptable representative has provided informed consent when the subject is legally too young to provide informed consent and the subject has provided written assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated, except for standard of care local testing as permitted per Section 21.3.

111 Age greater than or equal to 1 month to less than 21 years. Subjects greater than or equal to 18 years must have had their original diagnosis at less than 18 years of age.

112 Subjects must be diagnosed with relapsed or refractory relapsed ALL.

113 Subjects must have a documented first remission, less than 5% blasts in the bone marrow (M1 bone marrow) and no evidence of extramedullary disease.

114 T-cell ALL with bone marrow relapse (defined as greater than or equal to 5% leukemia blasts in bone marrow) or refractory relapse with or without extramedullary disease.

OR

B-cell ALL with bone marrow relapse or refractory relapse (defined as greater than or equal to 5% leukemia blasts in bone marrow) after having received a targeted B-cell immune therapy (eg, blinatumomab, inotuzumab, or a CAR-T therapy) with or without extramedullary disease.

115 Adequate liver function: bilirubin less than or equal to 1.5 x upper limit of normal (ULN), alanine aminotransferase (ALT) less than or equal to 5 x ULN.

116 Adequate renal function: serum creatinine less than or equal to 1.5 x ULN or glomerular filtration rate (GFR) greater than or equal to 70 mL/min/1.73 m^2; or for children less than 2 years of age, greater than or equal to 50 mL/min/1.73 m^2.

117 Adequate cardiac function: shortening fraction greater than or equal to 30% or ejection fraction greater than or equal to 50%

118 Karnofsky (subjects greater than or equal to 16 years of age) or Lansky (subjects 12 months to less than 16 years of age) performance status greater than or equal to 50%.

119 Subjects must have fully recovered from the acute toxic effects of all previous chemotherapy, immunotherapy, or radiotherapy treatment before enrollment (for example: recovery from gastrointestinal toxicity may occur more rapidly than less reversible organ toxicities such as sinusoidal obstruction syndrome or non-infectious pneumonitis, for serious prior toxicities recommend discussion with Amgen medical monitor).

120 Life expectancy of greater than 6 weeks per investigator`s judgment at time of screening.

21.2 Exclusion Criteria

Subjects are excluded from the phase 2 part of the study if any of the following criteria apply:

211 Prior treatment with carfilzomib.

214 Intolerance, hypersensitivity, or inability to receive any of the chemotherapy components of the VXLD regimen (or acceptable substitutes as listed in Section 22.1.2.1). An exception is allowed for allergy to asparaginase products if Erwinia asparaginase is unable to be administered.

215 Autologous HSCT within 6 weeks prior to start of study treatment.

216 Allogeneic HSCT within 3 months prior to start of study treatment.

217 Active GVHD requiring systemic immune suppression.

218 Less than 30 days from discontinuation of immune suppressive therapy administered for the treatment of acute or chronic GVHD.

219 Isolated extramedullary relapse.

220 Positive bacterial or fungal infection within 14 days of enrollment (except for documented line infection, line has been removed, and blood culture after line removal is negative for 5 days prior to first dose of induction therapy). Antibiotics may be administered for prophylaxis as per institutional standards up to and after enrollment.

221 Subjects with less than 3 antibody half-lives since the last dose of monoclonal antibody (eg, 66 days for rituximab, 69 days for epratuzumab, inotuzumab for 36 days), prior to first dose of investigational product must be discussed with the Amgen medical monitor and may be allowed to enroll based on extent of disease or evidence of rapidly rising peripheral or bone marrow blast counts.

222 Cell-based immunotherapy (eg, donor leucocyte infusion, CAR-T cells, tumor vaccines) within 42 days prior to first dose of investigational product. If the Amgen medical monitor agrees, an exception may be granted to the 42-day requirement for subjects with rapidly rising peripheral or bone marrow blast counts.

223 Down's syndrome.

224 Presence of another active cancer.

225 History of grade greater than or equal to 2 pancreatitis within 6 months to screening

226 Unresolved toxicities from prior anticancer therapy, defined as not having resolved to CTCAE version 4.03 grade 1 or to levels dictated in the eligibility criteria apart from alopecia or toxicities from prior anticancer therapy that are considered irreversible and do not trigger another exclusion criterion (defined as having been present and stable for greater than 4 weeks)

227 Antitumor therapy (chemotherapy, investigational agents, molecular-targeted therapy) within 7 days of day 1 of induction. Exception: hydroxyurea to control peripheral blood leukemic cell counts is allowed until start of investigational product.

228 Active viral infection, including but not limited to cytomegalovirus (CMV), Hepatitis B infection with positive serum hepatitis surface antigen or hepatitis B DNA, HIV, Hepatitis C with detectable hepatitis C RNA. Subjects who have previously received a stem cell transplant must be screened for CMV infection, unless both subject and donor are known to be CMV negative.

229 Currently receiving treatment in another investigational device or product study, or less than 14 days since ending treatment on another investigational device or product study.

230 Uncontrolled arrhythmias or screening ECG with corrected QT interval (QTc) of greater than 470 msec.

231 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

232 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 6 months after the last dose of any study treatment or for 12 months after last dose of cyclophosphamide if administered during optional consolidation cycle.

233 Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for an additional 6 months after the last dose of any study treatment or for 12 months after last dose of cyclophosphamide if administered during optional consolidation cycle. Refer to Section 29 for additional contraceptive information.

234 Female subjects of childbearing potential with a positive pregnancy test assessed at Screening by a serum or urine pregnancy test.

235 Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use a condom with spermicide during treatment and for an additional 6 months after the last dose of any study treatment, even if they have undergone a successful vasectomy.

236 Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom with spermicide during treatment, for duration of pregnancy, and for an additional 6 months after the last dose of any study treatment.

237 Male subjects unwilling to abstain from donating semen or sperm during treatment and for an additional 6 months after the last dose of any study treatment.

238 Known allergy to captisol (a cyclodextrin derivative used to solubilize carfilzomib; for a complete listing of Captisol-enabled drugs, see the Ligand Pharmaceuticals, Inc. website).

21.3 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 27). Evaluations performed within 7 days of enrollment as part of routine medical care (eg, bone marrow aspirate/biopsy) may be used for screening assessments.

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF), including the outcome of any required discussion with the Amgen medical monitor.

Each subject who enters into the screening period for the study (within 7 days prior to day 1) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by IRT. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

21.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 3 times. Refer to Section 24.1.1.

22. Phase 2: Treatments

Study treatment is defined as any investigational product(s) or non-investigational product(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

A summary of the dosing and administration of each treatment is shown in Section 22.1.

22.1 Treatment(s) Administered

22.1.1 Investigational Product: Carfilzomib

22.1.1.1 Dosage Formulation

Carfilzomib will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

Carfilzomib is supplied as a sterile, lyophilized, white to off-white powder ready for reconstitution. It is supplied for single use in 50 mL Type 1 glass vials containing 60 mg of carfilzomib drug product with an elastomeric stopper and flip-off lid.

22.1.1.2 Dosage, Administration, and Schedule

Carfilzomib will be administered twice-weekly IV over approximately 30 (± 5) minutes as indicated in Table 15, Table 17, Table 19, and Table 21. The dose will be 20 mg/m^2 on day 1 of induction therapy and at 56 mg/m^2 for all subsequent doses during induction therapy and including all doses during consolidation therapy.

Each subject's first dose of carfilzomib will be calculated based upon baseline body surface area (BSA) using the Mosteller formula, including subjects less than 12 months of age. In subjects with BSA greater than 2.2 m^2, the dose should be capped based on a BSA of 2.2 m^2. The dose for each subject should not be revised unless the subject experiences a change in body weight of greater than 20% in which case the BSA and dose should be recalculated. The carfilzomib dose must be adjusted for certain toxicities, see Section 22.2.1.1, Table 24, and Table 25 for a list of specific dose modifications.

Carfilzomib will be administered as an IV infusion. Mechanical infusion pumps are recommended, but gravity-dependent infusions are permitted if the infusion duration can be reliably maintained.

The planned dose (mg/m^2), quantity administered (mg), start date/time, stop date/time, reason for change in planned dose, reason for dose change/withheld, reason for dose delay, reason for dose interruption and package lot number of carfilzomib are to be recorded on each subject's eCRF.

22.1.1.3 Intravenous Prehydration

Adequate hydration is required to mitigate the risks for TLS and pre-renal azotemia, which have been associated with carfilzomib. Prehydration with at least 125 mL/m^2/hour of IV fluid is required for 1 hour prior to carfilzomib administration; hydration management is otherwise at the investigator's discretion and should be appropriate for

the clinical situation. Pre-hydration for carfilzomib may be combined with pre-hydration for other study medications and is not in addition to any required hydration for other study medications.

22.1.2 Non-investigational Product: VXLD

22.1.2.1 Dosage Formulation

The components of VXLD (vincristine, daunorubicin, PEG-asparaginase, and dexamethasone) or protocol-approved alternative substitutes for these agents are commercially available. The description, how supplied, and storage instructions for each drug product are available in the associated prescribing information. The study staff is advised to refer to the prescribing information that is specific to the brand or formulation of the drug product being administered to subjects at their site.

Induction Chemotherapy Backbone (VXLD) for children greater than or equal to 12 months (see also Table 15). For infants less than 12 months, see modifications to VXLD dose and schedule listed below and in Table 17.

If carfilzomib window is adjusted, scheduled backbone therapy may be adjusted ± 3 days to align with carfilzomib at investigator's discretion.

- Daunorubicin, 60 mg/m^2 IV on day 2
  - Administer into a large vein as an infusion over 15 to 60 minutes as required by institutional practice.
  - Administration in conjunction with rapidly infusing D5W or normal saline is recommended.
  - Protect from sunlight.
- Dexamethasone 6 mg/m^2 per day - given orally BID (3 mg/m^2 per dose given twice daily) on days 1 to 21
  - IV administration is acceptable, if the subject is unable to tolerate oral administration.
  - Round the calculated dosage up to the nearest one half tablet or 0.1 mL.
- PEG asparaginase 2500 U/m^2 IV on days 4 and 18
  - Infuse over 1 to 2 hours in D5W or normal saline.
  - Rapid access to emergency medications (ie, epinephrine and methylprednisolone) during and for approximately 24 hours following dosage administration is strongly recommended.
  - See Section 8.4.9 for information regarding the substitution of Erwinia for PEG asparaginase.
  - Asparaginase erwinia chrysanthemi recombinant (RYLAZE) may be used in regions where approved and available as a replacement for PEG or Erwinia asparaginase. RYLAZE is administered at a dose of 25 mg/m^2 intramuscularly

on Monday, Wednesday, and Friday for 6 doses as a replacement of each single dose of pegaspargase. Dose modifications are similar to those for asparaginase in Section 8.4.9 with specific instructions in the United States label and in Table 23.

- Alternate asparaginase formulations, or doses lower than the protocol specified dose, may be given per local standard of care after discussion with the Amgen medical monitor.

Table 23. Dose Modification for RYLAZE

Adverse Reaction	Severity	Action
Hypersensitivity Reaction	Grade 2 Grade 3 to 4	• Treat the symptoms • Discontinue RYLAZE permanently
Pancreatitis	Grade 2 to 4	• Hold RYLAZE for elevations in lipase or amylase greater than 2 times the ULN, or for symptomatic pancreatitis. • Resume treatment when lipase and amylase are less than 1.5 times the ULN and symptoms are resolved. • Discontinue RYLAZE permanently if clinical necrotizing or hemorrhagic pancreatitis is confirmed.
Thrombosis	Uncomplicated thrombosis	• Hold RYLAZE • Treat with appropriate antithrombotic therapy • Upon resolution of symptoms, consider resuming RYLAZE, while continuing antithrombotic therapy.
	Severe or life-threatening thrombosis	• Discontinue RYLAZE permanently. • Treat with appropriate antithrombotic therapy.
Hemorrhage	Grade 3 to 4	• Hold RYLAZE • Evaluate for coagulopathy and consider clotting factor replacement as needed. • Resume RYLAZE with next scheduled dose if bleeding is controlled.
Hepatotoxicity	Total bilirubin greater than 3 times to less than or equal to 10 times the ULN	• Hold RYLAZE until total bilirubin levels decrease to less than or equal to 1.5 times the ULN.
	Total bilirubin greater than 10 times the ULN	• Discontinue RYLAZE, do not make up missed doses.

ULN = upper limit of normal.

- Vincristine 1.5 mg/m^2 (maximum 2 mg dose) IV on days 1, 8, 15, and 22
  - Administer as an IV push over 1 minute or as an infusion, in accordance with institutional practice.

CNS Treatment (According to age-based dosing presented in Table 6).

Preservative free forms of cytarabine, hydrocortisone, and methotrexate should be used for IT administration.

- IT chemotherapy in accordance with institutional practice given within 7 days before enrollment or on day 1
- CNS negative subjects: IT methotrexate given on day 8
- CNS positive subjects: IT Triple Therapy (cytarabine, hydrocortisone, and methotrexate) given on days 8, 15, 22, and 29. In regions where alternatives to hydrocortisone as the steroid component of triple IT therapy are used, sites may substitute according to local standard practice.

In regions where the components of VXLD are not available, the following substitutions are permitted:

- Daunorubicin
  - Doxorubicin (1 to 1 conversion from daunorubicin)
  - Epirubicin (1.2 mg epirubicin for each 1 mg of daunorubicin)
  - Idarubicin (1 mg idarubicin for each 6 mg of daunorubicin)
  - Daunorubicin may be omitted, at the investigator's discretion, for subjects enrolling less than 6 months from stem cell transplant or CAR-T therapy or subjects in third or higher relapse, or in refractory relapse if the subjects most recent salvage therapy included an anthracycline.
- PEG-asparaginase
  - L-asparaginase
    - Induction
      - For subjects greater than or equal to 12 months during induction, administer 9000 U/m^2 IM every Monday, Wednesday, Friday (M-W-F) for 9 doses starting on day 1 or closest to day 1 matching M-W-F schedule.
      - For infants greater than or equal to 6 to less than 12 months of age during induction, administer 6000 U/m^2 IM every M-W-F for 6 doses starting on day 8 or closest to day 8 matching M-W-F schedule.
      - For infants less than 6 months of age during induction, administer 5000 U/m^2 IM every M-W-F for 6 doses starting on day 8 or closest to day 8 matching M-W-F schedule.
    - Consolidation
      - For subjects greater than or equal to 12 months during consolidation, administer 6000 U/m^2 IM every M-W-F for 3 doses starting on day 14 or closest to day 14 matching M-W-F.
      - Infants do not receive asparaginase during consolidation.
  - Subjects that are allergic to L-asparagine may substitute an appropriate dose of Erwinia asparaginase as described in Section 8.4.9.

- If Erwinia asparaginase is not available, sites may elect to delete asparaginase treatment or may conduct desensitization procedure prior to administration of either PEG- or L-asparaginase, using a desensitization procedure acceptable to their site.

- Dexamethasone
  - Prednisone (20 mg/m^2 converts to 3 mg/m^2 dexamethasone)
  - Prednisolone (20 mg/m^2 for each 3 mg/m^2 dexamethasone)
  - Methylprednisolone (15 mg/m^2 for each 3 mg/m^2 dexamethasone)

22.1.2.1.1 Rationale for Change in VXLD Chemotherapy

Changes in the VXLD backbone compared with the phase 1 portion of the study is intended to reduce toxicity of the VXLD backbone as a result of changes to the patient population. Changes in the eligibility criteria for the phase 2 portion of the study require subjects with B-cell ALL to be more heavily treated prior to enrollment compared with the phase 1 portion of the study. In addition, the overall level of prior therapy for subjects who enrolled in the phase 1 portion of the study increased over time.

Treatment-related mortality with a 4-drug induction therapy such as VXLD in relapsed ALL with recent prior transplant, CAR-T therapy, or in subjects with refractory relapse is known to range from 12% to greater than 20% and is likely higher for subjects with combinations of these risk factors. For example, overall induction mortality was 1.4% for primary treatment, 6.3% for first relapse, and 20.8% for second relapse (Saarinen-Pihkala et al, 2006); treatment mortality was 12% (6 of 51 pediatric subjects) for refractory first relapse (von Stackelberg et al, 2011) and 20% for relapse within 6 months of stem cell transplant compared to 7.7% for relapses $>$ 6 months from transplant (Willasch et al, 2017).

In the phase 1 portion of the study, 10 subjects were treated with VXLD and carfilzomib at the RP2D of 56 mg/m^2. Two subjects who received recent stem cell transplant had early death during induction as a result of toxicity attributable to VXLD. In addition, subjects with refractory relapse, multiply relapsed, or recent stem cell transplant or CAR-T therapy rarely recover bone marrow function at the end of 4-drug induction such as VXLD.

Based on the review of phase 1 safety data, investigators have the option to eliminate anthracycline for certain groups of subjects based on elevated risk of unacceptable toxicity, including subjects within 6 months of a CAR-T or stem cell transplant, multiple

relapsed (greater than first relapse), or subjects with refractory relapse who received an anthracycline based therapy in their most recent treatment.

22.1.2.2 Dosage, Administration, and Schedule

During induction therapy VXLD will be administered as indicated in Table 15 and Table 17.

22.1.3 Non-investigational Product: Modified BFM

22.1.3.1 Dosage Formulation

The components of the modified BFM regimen (cytarabine, 6-mercaptopurine, cyclophosphamide, vincristine, and PEG-asparaginase) or approved alternative substitutes for these agents are commercially available. The description, how supplied, and storage instructions for each drug product are available in the associated prescribing information. The study staff is advised to refer to the prescribing information that is specific to the brand or formulation of the drug product being administered to subjects at their site.

Protocol-approved alternatives are provided in Section 22.1.2.1.

22.1.3.2 Dosage, Administration, and Schedule

For children greater than 12 months of age, the modified BFM consolidation is identical to that in the phase 1b portion of the study, see Section 8.1.3 for details. During consolidation therapy modified BFM will be administered as indicated in Table 19 and Table 21 for children greater than or equal to 12 months or less than 12 months of age, respectively.

22.1.4 Non-investigational Product: Intrathecal Chemotherapy

22.1.4.1 Dosage Formulation

Intrathecal therapy is considered SOC and the components (methotrexate, cytarabine, and hydrocortisone [or for regions where hydrocortisone is not used, steroid acceptable to the site]) are commercially available. The description, how supplied, and storage instructions for each drug product are available in the associated prescribing information. The study staff is advised to refer to the prescribing information that is specific to the brand or formulation of the drug product being administered to subjects at their site.

22.1.4.2 Dosage, Administration, and Schedule

During induction therapy and consolidation therapy age dependent doses of IT chemotherapy (and for regions where hydrocortisone is not used, steroid acceptable to the site) will be administered as indicated in Table 15, Table 17, Table 19, and Table 21.

For regions where the SOC for IT medication does not include steroid, that component may be omitted. Use of alternate IT regimens per local practice may be allowed after discussion with medical monitor.

22.1.5 Medical Devices

No investigational medical devices will be used.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

22.1.6 Other Protocol-required Therapies

The investigator will be responsible for obtaining supplies of the protocol-required therapies.

22.1.6.1 Tumor Lysis Syndrome

Subjects at high risk of tumor lysis should be assessed rapidly for evidence of symptomatic hyperleukocytosis, TLS, and coagulopathy.

- Relevant laboratory tests from the screening period include:
  - Complete blood count (CBC)
  - Serum electrolytes, including calcium and phosphorus
  - Creatinine
  - Blood urea nitrogen (BUN)
  - Uric acid

Continued monitoring of these laboratory values at intervals suitable to the clinical condition is required, until abnormalities have resolved or the risk has abated. The risk for serious acute TLS usually subsides within the first 72 hours after initiation of therapy.

- If coagulopathy is suspected, monitoring of the following additional laboratory tests is strongly recommended:
  - Prothrombin and activated partial thromboplastin times
  - Fibrinogen
  - D-dimer
- To manage hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia, the following is required:

- Begin allopurinol
- Institutional guidelines for dosing and administration should be followed.
- Continue until peripheral blasts and extramedullary disease have been reduced.
- Treatment with Rasburicase should be considered for subjects with severe hyperuricemia, oliguria, or severe renal dysfunction.
  - Screening for glucose-6-phosphate dehydrogenase deficiency prior to Rasburicase administration is strongly recommended.
  - Institutional guidelines for dosing and administration should be followed.
- Hydrate at least 100 125 mL/m²/h to maintain urine output at least 3 mL/kg/h
  - Continue until peripheral blasts and extramedullary disease have been reduced.
  - Institutional guidelines for administration should be followed.
- If institutional practice includes alkalinization, alkalinize urine to maintain urine pH 6.5 to 7.5.
  - The regimen for alkalinizing urine is at the investigator's discretion.
  - Institutional guidelines for dosing and administration should be followed.
  - Alkalinization is not recommended when treating with Rasburicase.

22.1.6.2 Blood Products

- Blood products are provided at the discretion of the investigator.
- Institutional guidelines for administration should be followed.

22.1.6.3 Pneumocystis Jiroveci Prophylaxis

- Pneumocystis prophylaxis (PCP) must be provided throughout the study period.
- Oral administration of TMP SMX is preferred and is recommended to be administered twice weekly on consecutive days or per local standard of care. Alternative agents, such as dapsone, atovaquone, or aerosolized or IV pentamidine may be used if there is a documented contraindication to TMP SMX or significant concern for bone marrow suppression. The rationale for use of an alternative agent should be specified in the eCRF.
- Institutional guidelines for dosing and administration should be followed.
- For subjects with delayed recovery of peripheral blood counts investigators should consider replacing TMP-SMX after day 22 of induction with alternative therapy until recovery of bone marrow function, Atovoquone, aerosolized or IV pentamidine, dapsone, or other agent per institutional standards may be considered as short-term alternative to TMP-SMX.

22.1.6.4 Fungal Prophylaxis

- Fungal prophylaxis must be provided during periods of neutropenia (ANC less than 500/μL) from the Induction Cycle through the end of study treatment.

- Echinocandin (ie, caspofungin, micafungin, or anidulafungin) or amphotericin agents are acceptable.
  - Institutional guidelines for dosing and administration should be followed.
  - Provide treatment level doses, rather than prophylactic doses.
- Azole antifungal agents (ie, fluconazole, itraconazole, voriconazole, or posaconazole) given concurrently with vincristine may increase risk of neurotoxicity and their use as prophylaxis is not permitted.

22.1.6.5 Herpes Virus Prophylaxis

- Herpes simplex virus (HSV) prophylaxis must be provided throughout the study period for subjects with a history of documented or suspected HSV or varicella zoster virus infection.
- Acyclovir or valacyclovir are acceptable.
- Institutional guidelines for dosing and administration should be followed.

22.1.6.6 Bacterial Prophylaxis

- Bacterial prophylaxis during periods of neutropenia is strongly recommended, due to the high risk for serious bacterial infections in this population. Prophylaxis should continue until post-nadir myelorecovery and include appropriate coverage for gram-negative species and expanded gram-positive coverage.
- Institutional guidelines for dosing and administration should be followed.

22.1.6.7 Intravenous Immunoglobulin Supplementation

- Intravenous immunoglobulin (IVIg) supplementation for subjects with hypogammaglobulinemia (less than 500 mg/dL) is recommended, due to the high risk for infections in this population. IV Ig infusions should use concentrations no greater than 5 g/dL to avoid renal toxicity.
- Institutional guidelines for dosing and administration should be followed.

22.1.6.8 Central Line Care

- Measures to minimize the risk for catheter associated serious bacterial infections must be taken throughout the study period.
- The specific regimen for central line care should be consistent with institutional guidelines.

22.1.6.9 Fever and Neutropenia

22.1.6.9.1 Definition

- Fever and neutropenia is defined as a temperature greater than or equal 38.5°C on a single occasion, or greater than 38°C on 2 occasions within 2 hours, and an ANC less than 0.50 x 10^9/L.

22.1.6.9.2 Evaluation

- Blood cultures should be obtained from all lumens.
- Additional cultures (urine, cerebral spinal fluid [CSF], respiratory, etc) are obtained at the investigator's discretion and should be based on the specific clinical presentation.

- Chest radiographs and other imaging studies are obtained at the investigator's discretion and should be based on the specific clinical presentation.

22.1.6.9.3 Treatment

- Prompt empiric broad spectrum coverage for both gram-negative and gram-positive bacterial infection must be provided IV as soon as possible.
- Additional gram-negative coverage and glycopeptide agents are at the investigator's discretion and should be based on the specific clinical presentation.
- Antifungal, antiviral, and other additional agents are at the investigator's discretion and should be based on the specific clinical presentation.
- Institutional guidelines for dosing and administration should be followed.

22.1.6.9.4 Persistent or Recurrent Symptoms

- If fever persists for greater than 96 hours or recurs after 3 days of treatment, surveillance for fungal infections or other occult infections is strongly recommended.
  - Studies to consider include, but are not limited to:
    - Computed tomography (chest, sinuses, abdomen/pelvis, etc)
    - Bronchoalveolar lavage
    - Viral PCR (adenovirus, Epstein Barr virus, cytomegalovirus, COVID 19, etc)
- If not already part of the treatment regimen, treatment dose antifungal therapy should be initiated.
  - Although prohibited for prophylaxis, azoles may be provided at the investigator's discretion.
  - Institutional guidelines for dosing and administration should be followed.
- The addition of other antimicrobial agents should be seriously considered and is at the investigator's discretion.
  - Institutional guidelines for dosing and administration should be followed.

22.1.6.10 Myeloid Growth Factors

Investigators are strongly encouraged to administer prophylactic systemic antibiotics during periods of neutropenia (ANC less than 500/μL).

- Granulocyte colony stimulating factors may be administered starting 24 hours after the last dose of cytotoxic chemotherapy per investigators discretion and are recommended for subjects that are likely to have delayed neutrophil recovery, such as multiply relapsed, a history of prior stem cell transplant, or a history of delayed neutrophil recovery after cytotoxic chemotherapy based on observations from subjects in the phase 1 portion of this study. Institutional guidelines for dosing and administration should be followed.
- Administration of myeloid growth factors in response to severe infection or fever and neutropenia is at the investigator's discretion

22.1.6.11 Gastritis Prophylaxis

- Prophylaxis with either a histamine 2 (H2) blocker or proton pump inhibitor is required during the Induction Cycle.
- Continued administration of gastritis prophylaxis during the optional cycle of consolidation therapy is at the investigator's discretion.

22.1.6.12 Prevention and Management of Nausea and Vomiting

- Prophylactic antiemetic administration is strongly recommended when emetogenic chemotherapy, including IT therapy, is administered.
- The precise antiemetic regimen is at the investigator's discretion.
- Corticosteroid administration as part of the antiemetic regimen is prohibited.
- Institutional guidelines for dosing and administration should be followed.
- Intravenous fluids and/or nutrition support should be provided, if nausea or vomiting prevent adequate intake of fluids or nutrients.

22.1.6.13 Constipation Prophylaxis

- Administration of stool softeners and/or laxatives to prevent constipation is strongly recommended.
- The precise bowel regimen is at the investigator's discretion.
- Institutional guidelines for dosing and administration should be followed.

22.1.6.14 Mucositis

- Mucositis should be managed with IV hydration, hyperalimentation, and analgesia, as indicated. In addition, consider coverage with broad spectrum gram-positive and gram-negative empiric antibiotic therapy and empiric antiviral and antifungal therapy, as indicated.

22.1.6.15 Contraception

Contraception requirements are provided in Section 29.

22.1.6.15.1 Female of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered of childbearing potential:

1. Premenopausal female with 1 of the following:
   a. Documented hysterectomy
   b. Documented bilateral salpingectomy
   c. Documented bilateral oophorectomy
      Note: Site personnel documentation from the following sources is acceptable: 1) review of subject medical records, 2) subject medical examination, or 3) subject medical history interview.

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

22.1.6.15.2 Female Subjects

Female subjects of childbearing potential must agree to use one highly effective method of contraception (as described in the table below) during treatment and for an additional 12 months after the last dose of protocol-required therapies. Contraception must be in place at least 2 weeks prior to the first study treatment.

Highly Effective Contraceptive Methods for Female Subjects Failure rate of less than 1% per year when used consistently and correctly.
• Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal) • Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable) • Intrauterine device (IUD) • Intrauterine hormonal-releasing system (IUS) • Bilateral tubal ligation/occlusion • Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success) • Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence must be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)

If a female subject is suspected of being pregnant, the protocol-required therapies must be stopped immediately and may not be resumed until absence of pregnancy has been medically confirmed.

22.1.6.15.3 Male Subjects

If the male's sole sexual partner is of non-childbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study. The definition of non-childbearing potential is provided above.

Male subjects with a partner of childbearing potential must agree to not father a child during treatment and for an additional 6 months after the last dose of protocol-required therapies.

Contraceptive options for male subjects include:

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies). The reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject or
- Use a condom during treatment and for an additional 6 months after the last dose of protocol-required therapies.

The female partner is to use an acceptable method of effective contraception such as: hormonal, IUD, IUS, female barrier method (diaphragm, cervical cap, contraceptive sponge [a female condom is not an option because there is a risk of tearing when both partners use a condom]). Male subjects must not donate sperm during treatment and for an additional 6 months after the last dose of protocol-required therapies.

Male subjects with a pregnant partner must practice sexual abstinence or wear a condom to prevent exposure of the unborn child to study drugs through semen.

22.1.6.15.4 Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical trials include: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to fetus if they become pregnant or father a child during treatment and for 6 months after the last dose of protocol-required therapies.

22.1.7 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device(s) after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors or partners for

whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

This includes any investigational product provisioned and/or repackaged/modified by Amgen including carfilzomib.

Any product complaint(s) associated with an investigational product supplied by Amgen are to be reported.

22.1.8 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

- The following treatments are excluded:
  - Marketed or investigational anticancer therapeutics that are not a component of this treatment regimen
  - Radiotherapy, except as clinically indicated for control of life-threatening symptoms related to CNS or mediastinal mass
  - Investigational agents for non-neoplastic conditions
  - See Section 22.1.6.4 and Section 22.1.6.9.4, and Section 22.1.6.10 for instructions about azole antifungal agents and myeloid growth factors, respectively, as their administration is restricted to certain circumstances.

22.2 Dose Modification

22.2.1 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Carfilzomib may be discontinued, temporarily delayed, or dosage temporarily reduced, in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants discontinuation, temporary delay or dose reduction. Carfilzomib must be temporarily interrupted and/or reduced or discontinued based on toxicities indicated in Table 25. Dose levels for decreasing carfilzomib are in Table 24. Subjects requiring a temporary dose interruption due to infection related adverse events may resume treatment at the same dose once the subject is stable and the infection is under control. Subjects that require dose reduction due to toxicities listed in Table 25 should remain at that reduced dose level (unless a subsequent dose reduction is required) until the end of the cycle.

Subjects continuing on to the optional consolidation therapy may be rechallenged with same dose carfilzomib at the investigator's discretion. If the toxicity recurs after the subject is rechallenged, omit until improved to grade indicated in Table 25 and then resume at 1 dose level lower as shown in Table 25. For the phase 2 part of the study, the guidance provided in the dose modification table (Table 25) supersedes guidance for carfilzomib dose reductions provided in Sections 8.2 and 8.4.1.

Dose modification guidelines for chemotherapy agents that are part of the VXLD regimen are provided in Sections 8.4.2 through 8.4.10.

Table 24. Example Dose Decrements for Carfilzomib

Nominal Dose (mg/m^2)	Reduced Carfilzomib Doses (mg/m^2)		
	Dose -1	Dose -2	Dose -3
56	45	36	27

Table 25. Dose Modification Table for Carfilzomib

Symptom/Sign/Investigation	**Recommended Action** **Carfilzomib**
Tumor lysis syndrome	
Therapy is not interrupted for tumor lysis syndrome unless there are life-threatening clinical or laboratory findings	See Section 22.1.6.1 for management recommendations
≤ grade 3	No adjustment
grade 4 life-threatening sequelae	Withhold carfilzomib until resolution to < grade 4 then resume at full dose
Thrombotic microangiopathy (TMA)	
Fever, microangiopathic hemolytic anemia, thrombocytopenia, renal failure, neurologic changes	If the diagnosis is suspected, withhold carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If TMA is confirmed, permanently discontinue. If the diagnosis of TMA is excluded, carfilzomib dosing may be resumed.
Cardiovascular and pulmonary	
Congestive heart failure (CHF): New onset or worsening CHF	Regardless of the attribution to study drug, hold the carfilzomib until resolution of CHF or return to baseline. Appropriate medical management should be initiated. If no resolution or return to baseline after 4 weeks, permanently discontinue carfilzomib.
< grade 3	Once congestive heart failure resolves or returns to baseline, resume at full dose.
≥ grade 3	Once CHF resolves or returns to baseline, reinstate carfilzomib at 1 dose level reduction.
Pulmonary Toxicities: Noninfectious interstitial lung disease, acute respiratory failure, ARDS (grade > 3)	Withhold carfilzomib until resolved to grade 1 or baseline. Resume at 1 level dose reduction

Hypertension (defined based on blood pressure measurements adjusted for children per standard pediatric practice, mean of 3 resting measurements). General guidelines for management of hypertension per American Association of Pediatrics (AAP) are provided in Flynn et al, 2017. Management of hypertension should be according to AAP guidelines or per institutions standard practice.	
grade < 3	Continue at same dose if initiation of appropriate treatment controls hypertension per institutional practice
grade ≥ 3	Withhold carfilzomib until blood pressure returns to normal or baseline. Initiate appropriate anti-hypertensive therapy prior to resuming therapy at 1 dose level reduction
Pulmonary hypertension (grade > 2)	Withhold carfilzomib until resolution to grade 1 or baseline and restart at 1 dose decrement.
Venous thrombosis/embolism grade ≥ 3	Withhold dose and adjust anticoagulation regimen; resume at full dose once anticoagulation has been optimized per treating investigators discretion.
Infections and infestations	
Infection grade 4	• Withhold carfilzomib until the infection is controlled and signs of cardiopulmonary instability have resolved. • If subject has competed day 22 chemotherapy recommend initiation of granulocyte colony stimulating factor (GCSF) 24 hours after last dose of cytotoxic chemotherapy • If subject has not competed day 22 chemotherapy consider omitting day 22 therapy and initiating GCSF based on risk benefit assessment
Hepatitis B reactivation	• Withhold carfilzomib until infection is adequately controlled • Resumption of carfilzomib may be considered in subjects whose hepatitis B reactivation is controlled and where the benefits of study therapy outweigh the risks
Hepatic dysfunction and related investigations	
grade ≥ 3 elevation in bilirubin (≥ 3 x ULN), ALT and/or AST (> 5 x ULN)	• If attributed to carfilzomib withhold until resolution to baseline and monitor twice weekly. Resume carfilzomib with 1 dose level reduction for remainder of cycle, if drug-induced hepatoxicity is excluded. • If reduced dose is tolerated for the remainder of the cycle, the dose may be re-escalated to full dose in next cycle (consolidation) if applicable and if drug induced hepatotoxicity is excluded.
• Drug induced hepatotoxicity attributable to carfilzomib	• Discontinue carfilzomib
Peripheral neuropathy	
Grade 3 or grade 2 with pain	If attributed to carfilzomib, withhold until resolved to $\leq$ grade 2 without pain, then resume carfilzomib at 1 dose level reduction.
Grade 4	Discontinue

Posterior reversible encephalopathy (PRES)	
Variable combination of altered mental status, vision changes, seizure, hypertension, headaches	If PRES is suspected, withhold carfilzomib. Evaluate with neuroradiological assessment for radiographic evidence of PRES. If diagnosis is confirmed, permanently discontinue carfilzomib. If diagnosis excluded and clinically appropriate, may resume at previous dose.
Dyspnea	
Dyspnea (grade ≥ 2)	Withhold carfilzomib until resolution to grade 1 or baseline, then resume at 1 dose decrement. If caused by another adverse event listed in this table, follow recommendations for that adverse event.
Renal dysfunction	
CrCl ≥15 mL/min/1.73 m^2	Full dose, unless the reduction is to ≤ 50% of baseline clearance then withhold dose and monitor renal function until recovery, resume at same dose
CrCl < 15 mL/min/1.73m^2 (grade 4) not requiring dialysis	Withhold dose and monitor. If toxicity is due to carfilzomib, reduce dose by 1 dose level when renal function recovers to 25% of baseline. If renal toxicity is not related to carfilzomib, resume dose at the discretion of the investigator.
CrCl < 15 mL/min/1.73m^2 (grade 4) requiring dialysis	Withhold dose until CrCl returns to ≥ 15 mL/minute then resume same dose. If dialysis required use the maximal dose of 20 mg/m^2 and administer carfilzomib after dialysis.
Other non-hematologic toxicity	
Any drug-related grade ≥ 3 non-hematologic toxicity not previously listed	For carfilzomib attribution, withhold carfilzomib until toxicity resolves to ≤ grade 1 or baseline, resume at 1 dose level lower and complete cycle
Progressive multifocal leukoencephalopathy (PML)	
New or worsening neurologic, cognitive or behavioral signs or symptoms that may be suggestive of PML	If PML is suspected, withhold administration of carfilzomib; patients should be promptly referred to a specialist and appropriate diagnostic testing should be initiated. Discontinue carfilzomib if PML diagnosis is confirmed.

22.2.1.1 Amgen Investigational Product: Carfilzomib

The reason for dose change of carfilzomib is to be recorded on each subject's eCRF.

22.2.1.2 Amgen/Non-Amgen Non-Investigational Product: VXLD, Modified BFM, and Intrathecal Chemotherapy

The reason for dose change of any non-investigational product(s) is to be recorded on each subject's eCRF(s).

22.2.1.3 Dose Modifications for Modified Infant Consolidation

Follow guidance in Sections 8.4.2 to 8.4.10 with the following exceptions:

Cyclophosphamide

In presence of macroscopic hematuria, omit. If there is a history of previous significant hematuria, hydrate before cyclophosphamide until specific gravity is less than 1.010 and hydrate at 125 mL/m^2/hr for 24 hours after dose. Monitor for adequate urine output as per institution guidelines. Give IV mesna at a total dose that is 60% of the cyclophosphamide dose divided to 3 doses (eg, if the cyclophosphamide dose is

1000 mg/m^2, the total mesna dose is 600 mg/m^2 or 200 mg/m^2/dose). Give the first mesna dose 15 minutes before or at the same time as the cyclophosphamide dose and repeat 4 and 8 hours after the start of cyclophosphamide. This total daily dose of mesna can also be administered as IV continuous infusion. The continuous infusion should be started 15 to 30 minutes before or at the same time as cyclophosphamide and finished no sooner than 8 hours after the end of cyclophosphamide infusion.

Cytarabine (IV or SC)

Subjects should have ANC greater than or equal to 300/μL and platelets greater than or equal to 30 000/μL to start each 4-day cytarabine block. Once a 4-day block has started, do not interrupt for uncomplicated myelosuppression.

Do not withhold cytarabine for fever if it is likely to have been caused by the cytarabine. Obtain blood cultures if a central line is present. For rash or conjunctivitis, withhold for grade 3 to 4 toxicity until resolved. Make up missed doses and consider concurrent treatment with hydrocortisone or dexamethasone, and/or with dexamethasone ophthalmic drops for conjunctivitis.

Mercaptopurine

If possible, mercaptopurine therapy should not be interrupted. If a cytarabine block has to be postponed or interrupted, then mercaptopurine should also be interrupted. Omitted mercaptopurine doses should be made up until the planned cumulative total dose 1680 mg/m^2 (60 mg/m^2 x 28 doses) for subjects greater than or equal to 12 months, 1260 mg/m^2 (45 mg/m^2 x 28 doses) for infants 6 to less than 12 months, 1120 mg/m^2 (40 mg/m^2 x 28 doses) for infants less than 6 months.

IT Methotrexate

Systemic toxicity: the dosage for IT methotrexate will not be reduced for systemic toxicity (myelosuppression, mucositis, etc). Instead, leucovorin may be used at a dose of 5 mg/m^2/dose every 12 hours x 2 doses, beginning 48 hours after the IT therapy has been delivered. This may reduce the risk of worsening already existent myelosuppression (ANC less than 500/μL) or mucositis. Do not administer leucovorin solely to prevent myelosuppression.

22.3 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product during the study are provided separately.

22.4 Measures to Minimize Bias: Randomization and Blinding

22.4.1 Method of Treatment Assignment

Subjects who meet eligibility criteria will be assigned to treatment with CFZ-VXLD.

22.4.2 Blinding

This is an open-label study; blinding procedures are not applicable.

22.5 Treatment Compliance

Administration of IV or SC medicinal products will occur at the study center. Oral medication may be administered at the center or dispensed for self-administration at home. Subjects/subject's legal representatives are to document all administered doses and missed doses in a medication diary for all study-required medication taken at home.

22.6 Treatment of Overdose

There is no specific antidote for carfilzomib. Therapy for overdose involves monitoring and management of acute side effects until the subject is stable.

22.7 Prior and Concomitant Treatment

22.7.1 Prior Treatment

Prior therapies for ALL that were being taken/used from time of diagnosis through the signing of the informed consent will be collected.

22.7.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 22.1.8.

Concomitant therapies are to be collected from time of informed consent through the safety follow-up visit.

23. Phase 2: Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 23.1 and 23.2.

23.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 14) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 27.

Reasons for early removal from protocol-required investigational product(s) or procedural assessments (during induction and/or consolidation) may include any of the following:

- Decision by **s**ponsor
- Lost to follow-up
- Adverse Event
- Subject Request
- Subject or their legally acceptable representative withdraws consent for study treatment
- Requirement for alternative therapy
- Noncompliance with study procedures, including administration of prohibited medications
- Pregnancy
- Death
- Ineligibility determined
- Protocol Deviation
- Disease Progression

23.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject, or legal guardian, does not wish for the subject to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject, or legal guardian, appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 30 for further details). Refer to the Schedule of Activities (Table 14) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

23.2.1 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

23.3 Lost to Follow-up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

- For subjects who are lost to follow-up, the investigator can search publicly available records where permitted to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

24. Phase 2: Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Section 17.11.2).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

24.1 General Study Periods

24.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject/legal representative has signed the informed consent form, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. The screening window is up to 7 days before day 1.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 21.4) as applicable. Bone marrow aspirate must be obtained and a morphologic diagnosis of relapsed or refractory ALL must be determined prior to study enrollment. In the event that aspirate cannot be obtained, diagnosis may be made by biopsy. It is not necessary for the results of immunophenotyping or cytogenetic studies to be available prior to enrollment or the initiation of study treatment.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening up to 3 times.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 7 day/week screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins

more than 7 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

24.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Section 17.11.2). The date of the first dose of carfilzomib is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Investigational products are to be administered after all other assessments have been completed, unless otherwise specified, during each visit that it is required.

24.1.3 Safety Follow-up

The safety follow-up visit is to be performed 30 days after the last dose of protocol specified systemic anti-leukemia therapy in induction or consolidation whichever is later, or prior to next therapy following induction if not proceeding to optional consolidation, or prior to next therapy after consolidation.

24.1.4 Long-term Follow-up

After discontinuation from study treatment, subjects are to continue follow-up every 12 weeks for up to 2 years after the safety follow-up, death, subject is lost to follow-up, or the sponsor decides to close the study, or the last living subject completes the safety follow-up, whichever comes first. The information collected in this phase includes relapse date (if applicable), date of subsequent treatment with stem cell transplant (if applicable), date of treatment start with subsequent immune therapy, if applicable (blinatumomab, inotuzumab, or CAR-T), and vital status.

Disease response assessments, including subsequent ALL therapies, and survival information will be collected as indicated in the Schedule of Activities.

24.1.5 End of Study for Individual Subjects

The end of study for each subject is defined as the date of whichever of the following occurs first: subject completes the safety follow-up or long-term follow-up (whichever is later), subject discontinues the study due to death, subject is lost to follow-up, subject withdraws full consent from the study, last surviving subject enrolled in the study completes the safety follow-up triggering the end of the study, or the sponsor decides to close the study.

24.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

24.2.1 General Assessments

24.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC and Amgen approved informed consent before any study-specific procedures are performed.

24.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact on [redacted] and PK of the protocol-required therapies.

24.2.1.3 Medical History

Medical history will include collecting information on the subject's significant medical conditions, prior surgeries, and neuropathy history, dating back to the original diagnosis. Record all findings on the medical history eCRF. The current toxicity grade will be collected for each condition that has not resolved. Cardiovascular risk factors, which include family history of cardiovascular disease and smoking history, will also be collected.

In addition to the medical history above, ALL history must date back to the original diagnosis.

24.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

24.2.1.5 Physical Measurements

Height (in centimeters) should be measured without shoes. Weight (in kilograms) should be measured without shoes.

Body surface area should be calculated using the Mosteller Formula (Mosteller, 1987):

BSA (m^2) = ([Height(cm) × Weight(kg)]/3600) ½.

24.2.1.6 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of tobacco.

24.2.1.7 Karnofsky and Lansky Performance Status

Performance status will be assessed by the Karnofsky and Lansky scales (Appendix F). Performance status will be included in the physical examination (Section 24.2.1.4).

24.2.2 Efficacy Assessments

24.2.2.1 Response Assessment

Response assessments will be performed by the investigator at the timepoints indicated in the Schedule of Activities (Table 14, Table 16, Table 18, and Table 20). Bone marrow aspiration, lumbar puncture, extramedullary disease assessment, and CBC with differential and platelets will be performed to assess the disease status. Lumbar puncture to assess disease status will not be required after the second lumbar puncture for subjects who are CNS-negative. Subjects who are CNS-positive must have 2 consecutive lumbar punctures without evidence of leukemia, before lumbar puncture is no longer required for assessment of disease status.

During the recovery window from day 29 through day 45 (day 36 to 50 for infants) after induction or consolidation if applicable, peripheral blood counts with differential should be obtained weekly and on the day of the bone marrow assessment. If clinically feasible subjects should be allowed to recover marrow function and peripheral blood counts prior to performing the bone marrow. Count recovery within 7 days of the bone marrow may be used to assign response status, assuming all other requirements for response are met. In subjects that do not proceed to consolidation or next therapy before day 45 (day 50 for infants), peripheral blood counts with differential should be obtained on day 45 (day 50 for infants). In the event that multiple bone marrow assessments are performed during the day 29 to 45 (or day 36 to 50 for infants) window and multiple assessments of M1 (less than 5% blasts) or NE, the investigator should report the best response level with the order from best to worst being CR, CRp, complete remission with partial hematologic recovery (CRh), CRi, NE. Subjects whose response at any time during the response window is SD or PD should retain that response.

A portion of the bone marrow collected at the time of these response assessments will be submitted to a central laboratory, for determination of MRD. Additional stained slides of bone marrow aspirate (or biopsy if aspirate is not available) and peripheral blood will be submitted to central laboratory for histological examination, full instructions for collection and submission are provided separately.

The criteria for determining treatment response are defined in Table 26.

Table 26. Treatment Response Definitions

Complete remission (CR)	- Attainment of M1 bone marrow status (less than 5% blasts in a bone marrow aspirate and at least 200 cells counted) with no evidence of circulating blasts or extramedullary disease - Recovery of peripheral counts: • ANC greater than or equal to 1000/μL • Platelets greater than or equal to 100 000/μL
Complete remission without platelet recovery (CRp)	- Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease - Recovery of peripheral counts: • ANC greater than or equal to 1000/μL • Platelet count less than 100 000/μL
Complete remission with partial hematologic recovery (CRh)	- Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease - Recovery of peripheral counts: • ANC greater than or equal to 500/μL but less than 1000/μL • Platelet count greater than or equal to 50 000/μL but less than 100 000/μL
Complete remission with incomplete hematologic recovery (CRi)	- Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease - ANC and platelet counts not fulfilling criteria for CRh, CRp, or CR
Stable disease (SD)	Subject has an evaluable bone marrow and does not satisfy the criterion for PD, fails to qualify for CR, CRp, CRh, or CRi
Non-evaluable	Subject does not qualify for PD based on peripheral blood blasts or extramedullary disease progression, and neither bone marrow aspirate or biopsy are adequate for pathological evaluation
Progressive disease (PD)	An increase from baseline (or nadir) of greater than or equal to 25% in bone marrow blasts, an absolute increase in the number of circulating leukemia cells of at least 5000 cells/μL, development of new sites of extramedullary disease, or a greater than or equal to 50% increase in size of previously involved sites from nadir

ANC = absolute neutrophil count; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; CRp = complete remission with incomplete recovery of platelets; PD = progressive disease; SD = stable disease
Note: When criteria are met for more than 1 response level the response level to report is the one indicating the highest bone marrow recovery with the order of recovery being CR > CRp > CRh > CRi. When criteria are met for both CRi and blast-free marrow, CRi should be reported.
Reference: NCCN, 2022; Shallis et al, 2021

24.2.2.1.1 Bone Marrow Aspirate

Bone marrow aspirates will be obtained for morphologic diagnosis of relapsed or refractory ALL. Stained aspirate slides from the same pull used by the local laboratory to determine response will be submitted for central laboratory histological review to evaluate response.

Bone marrow aspirate must be obtained and a morphologic diagnosis of relapsed or refractory ALL must be determined prior to study enrollment. In the event that aspirate cannot be obtained, diagnosis may be made by biopsy. It is not necessary for the results of immunophenotyping or cytogenetic studies to be available prior to enrollment or the initiation of study treatment. Bone marrow status definitions are provided in Table 2. The results of the local laboratory are applicable for inclusion into the study and to start study treatment if the results of the central laboratory are not yet available at the time these decisions are made.

The priority order of collection for the screening bone marrow aspirate sample, based on the volume and quality of sample obtained:

- Morphological diagnosis
- MRD by NGS centrally
- MRD by flow cytometry/PCR locally

24.2.2.1.2 Minimal Residual Disease Assessment

MRD assessment will be conducted in a central laboratory using next generation sequencing (NGS) by Adaptive. MRD testing as needed for clinical care may be done by a local laboratory using PCR or NGS and/or flow cytometry.

Bone marrow obtained during screening will be submitted to a central laboratory to facilitate the analysis of MRD by NGS. If adequate bone marrow aspirate for MRD cannot be collected, peripheral blood will be obtained prior to treatment and stored for [redacted] Bone marrows performed as part of routine medical care may be used for central lab MRD assessment.

Sites that perform local assessment for MRD at end of induction and/or consolidation are asked to report the result and method of assessment on the appropriate CRF. These data will be used for [redacted] (additional details will be provided in the statistical analysis plan [SAP]).

24.2.2.1.3 Lumbar Puncture

Cerebrospinal fluid must be obtained prior to the initiation of study treatment and examination must include:

- Red blood cell (RBC) count
- White blood cell (WBC) count
- Differential
- Cytology

It is not necessary for central nervous system (CNS) status to be declared prior to the initiation of study treatment. CNS status must be declared prior to the second scheduled lumbar puncture, however, as this informs the treatment regimen from that day on. CNS status definitions are provided in Table 3.

Subjects with CNS 3 leukemia at baseline will be considered to be CNS-positive and treated accordingly. Subjects with CNS2 status are to be determined to be either CNS positive (CNS3) or negative (CNS1) according to local institutional practice. The schedule of IT therapy will be determined by the status declared by the site.

The first dose of IT chemotherapy may be given with the lumbar puncture obtained during screening or at the time relapse is determined if it occurs within 7 days of induction day 1, in accordance with institutional practice, and is considered to be part of day 1 study treatment, provided that study enrollment and the remainder of day 1 study treatment occur within the required timeframe.

24.2.2.1.4 Testicular Ultrasound

Ultrasound or physical exam. Institutions may substitute alternative methods based on standard of practice. Capture as positive or negative/resolved on the eCRF.

24.2.2.1.5 Chest Imaging

Chest X-ray or institutional standard. Positive or negative/ resolved on the eCRF.

24.2.3 Safety Assessments

Planned timepoints for all safety assessments are listed in the Schedule of Activities see (Table 14, Table 16, Table 18, and Table 20).

24.2.3.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature.

Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF.

24.2.3.2 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The ECG must include the following measurements: heart rate, QRS, QT, QTc, and PR intervals. The principal investigator (or eg, designated site physician, central reader) will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

24.2.3.3 Echocardiograms (ECHOs)

All subjects will have a baseline ECHO, including assessments of systolic and diastolic left ventricular function and right ventricular function.

Subjects with clinical symptoms of congestive heart failure during or after induction should have an echocardiogram to evaluate cardiac function prior to initiation of the optional consolidation.

24.2.3.4 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date and reported cause of death should be obtained.

24.2.4 Adverse Events and Serious Adverse Events

24.2.4.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

24.2.4.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and is described in Section 28.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent/assent through the safety follow-up visit or 30 days after the last dose of investigational product/protocol-required therapies, whichever is later, are reported using the Events CRF.

24.2.4.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent/assent through the safety follow-up visit or 30 days after the last dose of investigational product/protocol-required therapies, whichever is later, are reported using the Events CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee immediately and no later than 24 hours of the investigator's awareness of the event, as indicated in Section 28. The investigator will submit any updated serious adverse event data to the sponsor immediately and no later than 24 hours of it being available.

Since the criteria for the CTCAE grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life threatening status), it will be left to the investigator's judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.

24.2.4.1.3 Serious Adverse Events After the Protocol-required Reporting Period

During the long-term follow-up period, if the investigator becomes aware of serious adverse events suspected to be related to investigational product after the protocol-required reporting period (as defined in Section 24.2.4.1.2) is complete, then these serious adverse events will be reported to Amgen. The investigator will report serious adverse events to Amgen immediately and no later than 24 hours following the investigator's awareness of the event on the Events CRF.

There is no requirement to actively monitor study subjects after the study has ended with regards to study subjects treated by the investigator. However, if the investigator becomes aware of serious adverse events suspected to be related to investigational

product, then these serious adverse events will be reported to Amgen immediately and no later than 24 hours following the investigator's awareness of the event.

Serious adverse events reported after the end of the study will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

If further safety related data are needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 28.

24.2.4.1.4 Safety Endpoints that are Study Endpoints

Safety endpoints (eg, mortality) that are study endpoints are reported on the Events CRF. All endpoints that also meet the criteria of serious adverse events must also be transmitted to safety immediately and no later than 24 hours of the investigator's awareness of the event (refer to Section 28).

24.2.4.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

24.2.4.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 23.3). Further information on follow-up procedures is given in Section 28.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following awareness of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Events CRF.

24.2.4.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

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

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

24.2.4.5 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

24.2.4.5.1 Adverse Events of Special Interest

The events of special interest for this protocol include the following:

- **cardiac toxicity (cardiac failure, myocardial ischemia, myocardial infarction, and cardiac arrest)**
- **pulmonary toxicities (acute respiratory distress syndrome, acute respiratory failure, acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease)**
- **pulmonary hypertension**
- **dyspnea**
- **hypertension including hypertensive crises**
- **acute renal failure**
- **hemorrhage and thrombocytopenia**
- **tumor lysis syndrome (TLS)**
- **infusion reactions**

- **hepatic toxicity**
- **venous thromboembolism**
- **hepatitis B virus (HBV) reactivation**
- **thrombotic microangiopathy**
- **posterior reversible encephalopathy syndrome (PRES)**
- **progressive multifocal leukoencephalopathy**

Investigators should monitor subjects for signs and symptoms of these risks. These risks are monitored by the procedures and laboratory tests described in the schedule of activities (eg, vital signs, hematology and chemistry laboratories, ECG, echocardiogram, or other clinically indicated tests) and should be reported by the Investigator to Amgen as adverse events or serious adverse events as per requirements described above (Refer to the Schedule of Activities [Table 14, Table 16, Table 18, and Table 20]). The management of these risks is described in Table 25. For additional information on these adverse events of special interest and other potential adverse reactions of carfilzomib, please refer to the Carfilzomib Investigator's Brochure.

24.2.4.6 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and female partners of male subjects will be collected after the start of study treatment and until 6 months after the last dose of any study treatment or for up to 12 months if subject received cyclophosphamide in optional consolidation cycle.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 29.

Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 29.

24.2.5 Clinical Laboratory Assessments

Refer to Section 26 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 14, Table 16, Table 18, and Table 20.) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

Pregnancy Testing

A high sensitivity (urine or serum) pregnancy test should be completed at screening for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Form, see Figure 7). Refer to Section 29 for contraceptive requirements.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

Hepatitis B Testing

All hepatitis testing will be performed locally. All subjects will be tested at screening for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc), unless performed within 6 months of screening and there was no change in the subject's risk factors within these 6 months. Subjects with positive testing or a history of prior HBV infection should have consultation with a specialist and must have HBV-DNA testing at screening and again at safety follow up. Subjects that have received Hepatitis B vaccination with only anti-HBs positivity and no clinical signs of hepatitis do not require HBV-DNA monitoring. A repeat HBV-DNA should be obtained at SFU only in subjects that required HBV-DNA at screening.

24.2.6 Pharmacokinetic Assessments

All subjects will have pharmacokinetic samples assessed.

Blood samples will be collected for measurement of plasma concentrations of carfilzomib as specified in the Schedule of Activities (Table 14, Table 16, Table 18, and Table 20).

25. Phase 2: Statistical Considerations

25.1 Statistical Hypotheses

The primary hypothesis is that CFZ-VXLD is superior to standard-of-care with regards to CR rate. This corresponds to evaluating whether the 95% CI for adjusted odds ratio (OR) between CR rate of CFZ-VXLD subjects versus external control subjects excludes 1 for each phenotype (B-cell/T-cell) independently.

25.2 Sample Size Determination

The sample size was determined based on practical considerations and limited phase 1 data available as specified in Section 18.2.4. Due to the rarity of the patient population, a minimum of 50 B-cell subjects and a minimum of 30 T-cell ALL subjects are planned to be enrolled, in order to reach more than 70% power for testing the primary hypothesis for at least one phenotype at 2-sided alpha of 0.05, with an interim futility analysis.

The external control arm is expected to include **approximately 74** B-cell ALL subjects and **approximately 6**0 T-cell ALL subjects as per the **primary** analysis sets **(B-PAS/T-PAS)** included in Study 20180065. More details will be presented in the **S**tudy 20180065 protocol which will provide the data for the external control **arm**.

For selected objectives, the response and disease status for each subject will be derived by the sponsor based upon the local assessments and following the definitions included in Table 26.

Additionally, after appropriate propensity score adjustment, CR rate is expected to be 25% for B-cell and 15% for T-cell subjects from the external control arm, and approximately 60% for B-cell and 30% for T-cell subjects from CFZ-VXLD arm. As these estimates are based on data available so far, additional scenarios proposed for the experimental arm **CR rates and sample sizes** and the power**/external control sample sizes** expected in these cases are included in Table 27.

Table 27. Power Estimates Based on Various Scenarios for Sample Size and Hypothesized Relative Effect

Phenotype	Control Arm CRR	CFZ-VXLD Arm CRR	Control Arm Sample Size	CFZ-VXLD Arm Sample Size	Power[a]
B-cell	0.25	0.5	74	50	0.70
B-cell	0.25	0.55	74	50	0.85
B-cell	0.25	0.6	74	50	0.94
B-cell	**0.25**	**0.5**	**66**	**56**	**0.72**
B-cell	**0.25**	**0.55**	**66**	**56**	**0.86**
B-cell	**0.25**	**0.6**	**66**	**56**	**0.94**
B-cell	**0.25**	**0.5**	**62**	**60**	**0.71**
B-cell	**0.25**	**0.55**	**62**	**60**	**0.87**
B-cell	**0.25**	**0.6**	**62**	**60**	**0.95**
T-cell	0.15	0.3	60	30	0.24
T-cell	0.15	0.3	60	40	0.27

CFZ-VXLD = carfilzomib combined with VXLD; CRR = complete remission rate; VXLD = vincristine, dexamethasone, PEG-asparaginase, daunorubicin
[a] The power was adjusted **with** a factor of 0.9**9** due to **interim analysis for** futility.

The hypothesized treatment effect size was determined based on the covariates predictive of CR observed in the phase 1 portion of the trial and the CR rates reported in the literature for those characteristics. More details are presented in Section 18.2.4.

For each phenotype separately (B-cell/T-cell), H0 will be rejected at the primary analysis if the adjusted OR 95% CI from the propensity adjusted model is above 1. The power was estimated assuming that both treatment arms will be balanced with respect to baseline prognostic factors after propensity score adjustment, the control arm probability of CR (PoCR) will be consistent at the time of futility and primary analysis, the odds ratio of PoCR is 1 under H0, and the **power loss** is **at most** 0.0**1** under H1. The power was adjusted by a factor of 0.9**9** due to futility check.

Since the variance of the log odds ratio will be inflated with the IPTW-ATT method compared to a non-weighted model, the estimates were adjusted by a variance inflation factor of 1.4 obtained via simulation using data from the blinatumomab B-cell ALL pediatric US Study 20140228 and European Study 20120299. The inflation factor was selected as the empirical 95% CI upper limit using the sandwich estimator of the log odds ratio standard error. A grid search approach was used to estimate the sample size

needed for the test. For each candidate number of subjects for the test arm, the lower bound of the 95% CI of the odds ratio (incorporating variance inflation factor) for each possible pair of outcomes was calculated and compared with 1. Power was derived as the summation of the joint probabilities of those pairs of outcomes with a lower bound greater than 1. The R-script for power calculation is presented in SAP.

25.3 Analysis Sets, Subgroups, and Covariates

25.3.1 Analysis Sets

All analysis sets below will be analyzed for B-cell and T-cell phenotypes separately.

Additional details will be provided in the SAP.

25.3.1.1 Primary Analysis Set

The primary analysis set (PAS) will include subjects enrolled in the experimental CFZ-VXLD arm who received at least 1 dose of carfilzomib and all external control subjects included in the **B-PAS/T-PAS** defined in **the** Study 20180065 protocol. If external control subjects have multiple qualifying therapies, the **last qualifying** therapy will be chosen.

25.3.1.2 Safety Analysis Set

This analysis set will include subjects enrolled to the experimental CFZ-VXLD arm who received at least 1 dose of carfilzomib.

25.3.1.3 Per Protocol Analysis Set

This analysis set will include subjects enrolled to the experimental CFZ-VXLD arm who received at least 1 dose of carfilzomib and have no important protocol deviations as described in the SAP.

25.3.1.4 Interim Futility Analysis Set

The interim futility analysis set will include **approximately 60** subjects **(60%** of the planned number of subjects**)** from the experimental CFZ-VXLD arm who have received at least one dose of carfilzomib and have had the opportunity to complete a post induction response evaluation **and all available subjects from the external control arm by the time of interim analysis (as defined in Interim Analysis Set [T-IAS/B-IAS] of Study 20180065 protocol)**.

25.3.2 Covariates

Details of the covariates used in the propensity score modeling will be specified in the SAP.

25.3.3 Subgroups

Primary (CR) and selected secondary endpoints (CRh, CRp, and CRi), occurrence of a stem cell transplant or CAR-T therapy, EFS, and OS endpoints will be explored in the following subgroups of interest using the PAS; analyses will be performed separately for B-cell and T-cell ALL populations, unless otherwise specified. When there is not a sufficient number of subjects in the subgroup (ie, less than 20% of subjects in a treatment arm), relevant subgroups may be combined. In these subgroup analyses, all treatment arm subjects will receive a weight of 1 while control arm subjects will be IPTW-ATT weighted, with the same weights used for the primary analysis of the primary endpoint. Odds ratio and 95% CI will be produced for CR, CRh, CRp, and CRi. Hazard ratio (HR) and 95% CI will be produced for EFS and OS.

- History of prior HSCT
- History of primary induction failure
- Relapse time from HSCT
- Early T cell precursor phenotype (for T-cell phenotype only)
- Number of prior relapses
- Refractory qualifying relapse
- Cytogenetic risk (high risk = t(9:22), MLL translocation, hypodiploidy [< 44 chromosomes])
- Duration of first remission
- Age at diagnosis
- Sex
- Isolated BM at relapse
- Blast percent in marrow prior to the qualifying treatment
- Geographical region

The additional secondary endpoints: occurrence of a SCT or CAR-T, and MRD[-] status will be estimated in the same subgroups listed above, using the Safety Analysis set with no adjustment.

Additional details will be provided in the SAP.

25.3.4 Handling of Missing and Incomplete Data

Incomplete adverse event start dates, concomitant medications start or stop dates, death date, and missing baseline covariates will be imputed, and the details of missing data analysis and imputation rules will be described in SAP.

25.4 Statistical Analyses

The SAP will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 24.1.5.

25.4.1 Planned Analyses

25.4.1.1 Interim Futility Analysis

An interim analysis for futility will be conducted independently for each phenotype **T-cell and B-cell, respectively**. The analysis will occur after **at least 60** subjects **from the experimental arm** have received at least one dose of carfilzomib and had the opportunity to complete a post induction response evaluation.

The futility criterion will be derived such that the probability of futility is **at least 70% under H0 and the power loss is at most** 0.0**1** under H1, using a Bayesian predictive probability approach. Additional details are provided in the SAP.

25.4.1.2 Primary Analysis

The primary analysis for each phenotype will occur when the external control subjects **from B-PAS/T-PAS** have been selected and at least 100 enrolled subjects in the experimental arm have received at least one dose of carfilzomib and had the opportunity to complete a post induction response evaluation. All the available data on primary, secondary, and exploratory endpoints will be summarized at this time.

25.4.1.3 Final Analysis

The final analysis will occur after the end of the study for all subjects.

For each planned analysis, data will be subject to ongoing checks for integrity, completeness, and accuracy in accordance with the Data Management Plan with the expectation that all outstanding data issues are resolved ahead of the snapshot. The data will be locked to prevent further changes, and a snapshot of the locked database will be used in the analysis.

25.4.2 Methods of Analyses

25.4.2.1 General Considerations

Unless otherwise specified, the data will be presented for the Safety Analysis Set for B-cell and T-cell phenotypes analyzed separately.

Summary statistics will be provided for selected endpoints. For continuous variables, the number of subjects with non-missing data (n), mean, standard deviation, median,

minimum, and maximum will be presented. For discrete data, the frequency and percent distribution will be presented. Unless otherwise indicated, percentages will be calculated with respect to the number of subjects in the analysis set. Confidence intervals, when presented, will be constructed at the 2-sided 95% level. For binomial variables, exact distribution methods will be employed. The distribution of time-to-event endpoints will be summarized by Kaplan-Meier method when applicable.

Individual subject listings will be produced for selected endpoints using data recorded on the eCRFs or derived data.

25.4.2.2 Efficacy Analyses

Unless otherwise specified, all efficacy endpoints will be analyzed for B-cell and T-cell phenotype independently. The comparison analyses for CR, CRh, CRp, CRi, EFS, and OS endpoints will use the PAS, while for all the other efficacy endpoints, the Safety Analysis Set will be used. DOR will be analyzed only on responders from PAS (ie, subjects who reached a response of CR, CRp, CRh, or CRi).

Analyses of Primary Efficacy Endpoint

To evaluate the treatment effect with respect to the outcome of CR rate among pediatric relapsed or refractory ALL subjects, an external control arm representing pediatric ALL subjects receiving SoC without carfilzomib will be selected from the observational Study 20180065 according to the study protocol. For the primary analysis, the 20140106 study will be analyzed as a virtual randomized controlled trial comparing enrolled subjects treated with the CFZ-VXLD regimen versus the external control arm. The OR for the PoCR for CFZ-VXLD versus control will be estimated from a logistic regression model with inverse probability treatment weights for the average treatment effect of the treated (IPTW-ATT). These weights are derived for each CFZ-VXLD and control subject based on the propensity score for receiving CFZ-VXLD. Outlier weights will be trimmed if identified. Covariates that remain imbalanced after propensity score (PS) adjustment will be added in the analysis model as a sensitivity analysis. The 95% CI of the OR will be calculated using a robust sandwich covariance estimator and the lower bound of the 95% CI will be compared to 1. The CR rate and 95% CI by arm will also be estimated using the same logistic regression model.

Details of the PS analysis using IPTW-ATT approach will be specified in the SAP.

Estimated CR rate and 95% CI by arm along with OR (95% CI) of CR between CFX-VXLD and appropriated weighted external control using PS will be calculated via

the weighted logistic regression for the subgroups listed in Section 25.3.3. The same weights as those included in the primary analysis will be used for subgroup analyses. A forest plot will be produced for the estimated ORs (95% CIs).

The CFZ-VXLD subjects reaching CR at the end of Induction will also be summarized along with their Clopper Pearson 95% CI.

The sensitivity analyses will be considered and specified in the SAP.

Analyses of Additional Secondary Efficacy Endpoints

The proportion of safety analysis subjects and corresponding Clopper Pearson 95% CI will be estimated for the below secondary endpoints:

- MRD status using NGS less than 10^{-4} after induction therapy in subjects achieving CR
- Occurrence of a stem cell transplant or CAR-T, without an intervening relapse after protocol specified therapy
- CR, CRp, CRh, and CRi after induction therapy
- CR, CRp, CRh, and CRi after consolidation therapy
- MRD status using NGS less than 10^{-3} and less than 10^{-4} in subjects achieving CR, CRp, CRh, or CRi after induction and consolidation therapy**, separately**

The rate of CRp, CRh, and CRi at the end of induction per arm and the OR for CFZ-VXLD versus control will be estimated from a logistic regression model with IPTW-ATT adjustment along with their 95% CIs. This analysis will be performed following a similar approach and sensitivity analyses as for primary endpoint analysis.

EFS, OS, and DOR will be summarized by Kaplan-Meier method. The distribution of EFS/OS/DOR time including median and other quartiles will be summarized descriptively using the KM method (Klein and Moeschberger, 1997). The corresponding 95% CI for the median and other quartiles will be constructed using KM method with log-log transformation. Survival rates at 6, 12, 18, and 24 months will be estimated, and the corresponding 95% CIs will be calculated using the method of Kalbfleisch and Prentice (1980). The duration of the follow-up for OS/EFS will be estimated by reverse Kaplan-Meier method (Schemper and Smith 1996). KM curves will also be presented for OS and EFS. The HR for CFZ-VXLD vs external control arm will be derived for OS/EFS using Cox regression. This analysis will be adjusted following a similar approach and weights as for primary endpoint analysis. If the number of responders is small, the KM method may not provide reliable estimates **for DOR**; in this case, only descriptive statistics or listings will be provided.

Similar sensitivity analyses as for primary endpoint analysis will be considered for EFS/OS and are described in more detail in the SAP.

[redacted]

Details will be specified in the SAP amendment.

25.4.2.3 Safety Analyses

25.4.2.3.1 Analyses of Primary Safety Endpoint(s)

The safety analysis will include all data specified in Sections 25.4.2.3.2 through 25.4.2.3.10 and will be based on the safety analysis set analyzed for B-cell and T-cell separately.

Additionally, the safety data will be summarized by age categories.

25.4.2.3.2 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment-emergent adverse events will also be provided.

25.4.2.3.3 Laboratory Test Results

Actual values and change from baseline for laboratory measurements will be summarized and presented in subject listings. Additionally, the type, incidence, and severity of laboratory abnormalities will also be analyzed.

25.4.2.3.4 Vital Signs

Actual value and change from baseline for vital sign results including systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature will be summarized.

25.4.2.3.5 Physical Measurements

Actual value and change from baseline for the physical measurements including height, weight, and BSA will be summarized.

25.4.2.3.6 Electrocardiogram

The ECG measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect.

25.4.2.3.7 Echocardiogram

Echocardiogram, including assessments of systolic and diastolic left ventricular function and right ventricular function, will be summarized at baseline using descriptive statistics based on the Safety Analysis Set. Additionally, the unscheduled ECHO assessments (as clinically indicated, such as congestive heart failure) will be summarized using descriptive statistics, based on the number of adverse events that trigger the unscheduled ECHO assessments.

25.4.2.3.8 Exposure to Investigational Product

Descriptive statistics in terms of treatment duration (days), number of actual treatment days, total dose received, number of doses administered, average dose per administration, actual dose intensity, and relative dose intensity will be produced to describe the exposure to carfilzomib. Number (%) of subjects with carfilzomib dose modifications (missed doses, dose delays, dose reductions, and dose interruptions) will be summarized.

Descriptive statistics will be produced to describe the exposure to investigational product.

25.4.2.3.9 Exposure to Non-investigational Product

All the analyses planned for **investigational product** will be carried over for each drug in any chemotherapy combination and CNS treatment combination**, as specified in the SAP**. For CNS combination drugs (methotrexate cytarabine, and hydrocortisone), exposure will be summarized for CNS positive and negative separately.

25.4.2.3.10 Exposure to Concomitant Medication

The number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category as coded by the World Health Organization Drug (WHO DRUG) dictionary.

26. Phase 2: Clinical Laboratory Tests

The tests detailed in Table 28 will be performed by the local laboratory unless otherwise indicated.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 21.1 to 21.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 28. Phase 2 Analyte Listing

Chemistry	Hematology	Other Labs
Sodium	RBC	Coagulation tests:
Potassium	Nucleated RBC	INR
Chloride	Hemoglobin	aPTT
Bicarbonate	Hematocrit	Pancreatic function tests:
Total protein	MCV	Amylase
Albumin	MCH	Lipase
Calcium	MCHC	Viral studies:
Adjusted calcium	RDW	HBsAg
Magnesium	Platelets	anti-HBc
Phosphorus	WBC	anti-HBs
Glucose	Differential	Hepatitis C antibody
BUN or Urea	• Bands/stabs	CMV PCR[a]
Creatinine	• Segmented neutrophils	HIV[b]
Uric acid	• Eosinophils	Serum or Urine pregnancy
Total bilirubin	• Basophils	MRD (flow cytometry and/or PCR)
Direct bilirubin	• Lymphocytes	
ALP	• Monocytes	Central Laboratory:
AST (SGOT)	• Myeloblasts	Bone marrow aspirate for MRD by NGS
ALT (SGPT)	• Promyelocytes	
Creatinine clearance (calculated) or GFR	• Myelocytes	Pharmacokinetics
	• Metamyelocytes	[redacted]
	• Atypical lymphocytes	Stained bone marrow aspirate slides for histology
		Stained slides of peripheral blood

ALP = alkaline phosphatase; ALT = alanine aminotransferase; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CMV = cytomegalovirus; GFR = glomerular filtration rate; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MRD = minimal residual disease; NGS = next generation sequencing; RBC = red blood cell count; RDW = red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count

[a] required at screening for subjects with a history of prior stem cell transplant or known to be CMV positive.

[b] HIV assessment is recommended.

27. Phase 2: Study Governance Considerations

An independent Data Monitoring Committee (DMC) will review every 6 months all available safety and efficacy data for the safety analysis set. Additionally, the DMC will evaluate interim futility analysis. The DMC will communicate major safety concerns and recommendations regarding study modification or termination based on the safety and efficacy parameters to Amgen in accordance with the DMC charter. An Independent Biostatistics Group (IBG) will generate and provide regular reports to the DMC.

Records related to the closed-session meetings will be maintained by the IBG for the duration of the study. Amgen will be responsible for maintaining records concerning the

DMC open-session meeting and the DMC's recommendation. Records related to the closed-session meetings will be transferred and stored in the trial master file (TMF) at the conclusion of the study, and those related to the open-session will be filed on an ongoing basis in TMF. Further details are provided in the DMC charter.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Recruitment Procedures

Site staff will identify potential subjects from their existing patient population or may seek referral patients through existing professional networks or other community sources such as patient advocacy groups. All patient-facing materials must be reviewed/approved by the sponsor and the local IRB/IEC.

Informed Consent Process

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care

physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 23.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within 7 days from the previous informed consent form signature date.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

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

On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

Subject data should be kept in a secure location. Access to subject data will be limited to authorized individuals, as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Amgen complies with all relevant and applicable laws and regulations that protect personal information in order to ensure subject confidentiality and privacy. Subjects are designated by a unique subject identification number in the Sponsor's systems. The Sponsor uses access-controlled systems to house, review and analyze subject data. These systems are backed-up regularly to minimize the risk of loss of subject data; procedures are also defined for data recovery in the event of data loss. The Sponsor has standard operating procedures in place that restrict access to subject data to those who require access to this data based on their role and have also completed the

required training. These procedures also outline the process for revoking access to such data when it is no longer needed. In the event of a security breach, the Sponsor has procedures in place for notification of privacy incidents and to address these incidents, via its Business Conduct Hotline.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance, and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen’s review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

Case report forms must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

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

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the IRT system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment or certain demographic information).

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

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Retention of study documents will be governed by the Clinical Trial Agreement.

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product(s) by a separate protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

28. Phase 2: Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events will be defined in the SAP.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • For situations when an adverse event or serious adverse event is due to ALL report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic pancreatic cancer). Note: The term “disease progression” should not be used to describe the adverse event. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an adverse event or serious adverse event.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening

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

Requires in-patient hospitalization or prolongation of existing hospitalization

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

Results in persistent or significant disability/incapacity

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

Is a congenital anomaly/birth defect

Other medically important serious event

Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is 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 medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording
• When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF). • The investigator must assign the following mandatory adverse event attributes: o Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms); o Dates of onset and resolution (if resolved); o Did the event start prior to first dose of investigational product, other protocol-required therapies; o Assessment of seriousness; o Severity (or toxicity defined below); o Assessment of relatedness to investigational product, other protocol-required therapies, and/or study-mandated activity and/or procedures; o Action taken; and o Outcome of event. • If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event CRF. • It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Event CRF page. • If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

The Common Terminology Criteria for Adverse Events, version 4.03 which is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product(s), protocol-required therapies, and/or study-mandated activity and/or procedures and each occurrence of each adverse event/serious adverse event.
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.
- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.
- New or updated information will be recorded in the originally completed Event CRF.
- The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using a paper-based Serious Adverse Event Contingency Report Form (also referred to as the electronic Serious Adverse Event [eSAE] Contingency Report Form) (see Figure 6) within 24 hours of the investigator's awareness of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC system has been taken off-line, then the site can report this information on the paper-based Serious Adverse Event Contingency Report Form (see Figure 6). • Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.

Figure 6. Phase 2 Sample Electronic Serious Adverse Event Contingency Report Form (paper-based form)

AMGEN
Study # 20140106
carfilzomib

Electronic Serious Adverse Event Contingency Report Form

For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day ____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started (Day Month Year)	Date Ended (Day Month Year)	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? carfilzomib No / Yes	<<Device>> No / Yes	<<Device>> No / Yes	<<Device>> No / Yes	Outcome of Event •Resolved •Not resolved •Fatal •Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No							
				☐Yes ☐No							
				☐Yes ☐No							

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required/prolonged hospitalization; **04** Persistent or significant disability /incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted (Day Month Year)	Date Discharged (Day Month Year)

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

		Prior to, or at time of Event: Date of Initial Dose (Day Month Year)	Date of Dose (Day Month Year)	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
IP/Amgen Device:								
carfilzomib	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20140106 carfilzomib	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect		Continuing		Dose	Route	Freq.	Treatment Med	
			No✓	Yes✓	No✓	Yes✓				No✓	Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Test / Unit / Date (Day Month Year)											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20140106 carfilzomib	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

29. Phase 2: Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for males and females of childbearing potential are outlined in Section 21. Contraceptive use and methods should be consistent with local regulations for subjects participating in clinical studies.

Male and female subjects of childbearing potential should be advised of the pregnancy prevention requirements and the potential risk to the fetus if they become pregnant or father a child during treatment and for 6 months after the last dose of any study treatment or for 12 months after last dose of cyclophosphamide if administered during optional consolidation cycle for female subjects of child-bearing potential.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include documented hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Females with documented permanent infertility due to an alternate medical cause (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), can be considered not of childbearing potential.

Note: Bilateral tubal ligation/occlusion is not considered a permanent sterilization method.

Note: Documentation from the following sources is acceptable to provide confirmation of each sterilization method: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

A postmenopausal female is defined as:

- A woman of ≥ 55 years with no menses for 12 months without an alternative medical cause OR
- A woman age < 55 years with no menses for at least 12 months and with a follicle-stimulating hormone (FSH) level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); because an indirect interaction between oral contraceptives and PEG-asparaginase (or Erwinia)

cannot be ruled out, oral hormonal contraception is not recommended for female subjects during PEG- or Erwinia-asparaginase treatment

- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Use a condom with spermicide during treatment and for an additional 6 months after the last dose of any study treatment

The female partner of a male subject should consider using a highly effective method of contraception as stated above, or an acceptable method of contraception such as:

- Intrauterine device
- Intrauterine hormonal-releasing system
- Hormonal birth control method: pill, shots/injections, implants (placed under the skin by a healthcare provider), skin patches
- Female barrier method: diaphragm, cervical cap, contraceptive sponge for female subjects stated above (a female condom should not be used because there is a risk of tearing when both partners use a condom)

Note: If the male's sole female partner is of non-childbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study.

Collection of Pregnancy Information

<u>Female Subjects Who Become Pregnant</u>

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 6 months after last dose of any study treatment or up to 12 months if the female subject received cyclophosphamide in optional consolidation therapy.

- Information will be recorded on the Pregnancy Notification Form (see Figure 7). The form must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- After obtaining the female subject's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 6 months after last dose of any study treatment or up to 12 months if the female subject received cyclophosphamide in optional consolidation therapy. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event. Abnormal pregnancy outcomes (eg, spontaneous abortions, stillbirth, fetal death, congenital anomalies) will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 28. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment while pregnant (see Section 23.1 for details).

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 6 months after last dose of any study treatment after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 7) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).
- Males with pregnant partners or whose partners become pregnant during treatment and for an additional 6 months after last dose of any study treatment must practice sexual abstinence or use a condom through 6 months after last dose of any study treatment.

- The investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 6 months after last dose of any study treatment or up to 12 months if the female subject received cyclophosphamide in optional consolidation therapy.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's awareness of the event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 232.
- With the female subjects signed consent for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 6 months after last dose of any study treatment or up to 12 months if the female subject received cyclophosphamide in optional consolidation therapy.

Figure 7. Phase 2 Pregnancy and Lactation Notification Forms

Amgen Proprietary - Confidential

AMGEN Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20140106

Study Design: ☒ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (___)_____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject age (at onset):____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd___/ yyyy_____

Has the pregnant female already delivered? ☐Yes ☐No ☐Unknown ☐N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20140106

Study Design: ☒ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

30. Sample Storage and Destruction

Any blood [redacted] pharmacokinetics) sample collected according to the Schedule of Activities (Table 14, Table 16, Table 18, and Table 20) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand ALL, the dose response and/or prediction of response to carfilzomib, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, [redacted]

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood or bone marrow samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as

appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 27 for subject confidentiality.

Amendment 12

Protocol Title: Phase 1b/2 Study of Carfilzomib in Combination With Induction Chemotherapy in Children With Relapsed or Refractory Acute Lymphoblastic Leukemia

Amgen Protocol Number: Carfilzomib 20140106

EudraCT Number: 2014-001633-84

NCT Number: 02303821

Amendment Date: 28 August 2023

Rationale:

This protocol (dated 28 August 2023) is primarily being amended in the phase 2 portion only (Sections 1, 2, and 17.11 through 25) to update the interim analysis and primary analysis external control arm datasets, including updates to the number of subjects and impact on the statistical power. In addition, safety monitoring language was added in subsection 24.2.4.5.1, 'Adverse Events of Special Interest'. These changes were made to be consistent with Amendment 4 of the United States Food and Drug Administration (FDA) Written Request dated 01 August 2023. Changes including, but not limited to, the following were incorporated into the protocol:

- The approximate sizes of the external control arm datasets (Study 20180065) for the B-cell and T-cell primary analysis sets (B-PAS/T-PAS) were updated to approximately 74 B-cell acute lymphoblastic leukemia (ALL) subjects and approximately 60 T-cell ALL subjects from 90 and 70 subjects, respectively. Previous versions of the protocol included external control sample sizes that were larger than required to support the analysis.
- Language was added to the methods of interim analysis for futility to specify that the interim analysis will be done with the external control datasets that are available at time of interim. Previous versions of the protocol required the complete external control arm dataset to be available for interim analysis.
- "Full" Analysis was revised to "Final" Analysis. Definition of Final Analysis Sets (T-FAS/B-FAS) was removed, as not required. A definition of a Final Analysis

Set is not required due to the revisions to Interim and Primary Analyses. As revised, all external control data, as well as all 20140106 subjects, will be included in the Primary Analysis (and in the Final Analysis).

- Language was updated in the Primary and Interim Futility Analyses sections to align with the new approximate size of the external control arm datasets from Study 20180065.
- Power estimates were adjusted based on the expected approximate number of external control arm datasets provided above.
- Safety monitoring language was added in subsection 24.2.4.5.1, 'Adverse Events of Special Interest'.
- Additional changes were made for consistency and alignment throughout the protocol including, but not limited to, administrative, typographical, formatting, numbering, and abbreviation changes.

Amendment 11

Protocol Title: Phase 1b/2 Study of Carfilzomib in Combination With Induction Chemotherapy in Children With Relapsed or Refractory Acute Lymphoblastic Leukemia

Amgen Protocol Number 20140106 (formerly CFZ008)

EudraCT number 2014-001633-84

NCT number NCT 02303821

Amendment Date: 04 November 2022

Rationale:

The primary reasons for this protocol amendment are to:

- Allow the use of routine care procedures obtained within 7 days before enrollment to satisfy screening requirements. This is added due to a lack of clinical justification for repeating procedures that have no clinical benefit to the subject but expose the subject to potential risk. This flexibility is expected to reduce post-enrollment eligibility deviations and facilitate enrollment.
- Update minimum enrollment numbers of subjects with relapsed T-cell acute lymphoblastic leukemia (ALL) and with relapsed B-cell ALL based on current enrollment and health authority expectations. The minimum numbers of patients in the external control arm with relapsed B-cell ALL were also updated based on the status of incoming control arm data. The respective sample size estimates and expected power have been adjusted accordingly.

Additional changes are made to:

- Respond to site feedback regarding confusion between phase 1 and phase 2 sections of the protocol. The synopsis is revised to remove phase 1 information and expand phase 2 information. Revisions to bring focus to phase 2 of the protocol result in a re-numbering of Sections 17 and beyond (eg, former Section 17 is now Section 18). Section and table names are revised to include “Phase 2” for clarity (throughout protocol).
- Add details to define analytes used in the derivation of remission status for evaluation of the primary and secondary endpoints, and clarify that hematology and bone marrow aspirate/biopsy samples must be assessed locally
- Revise the description of the primary endpoint to clarify that there is a single endpoint of complete remission (CR). The previous amendment language included time window definitions for infants and children that could have been misinterpreted to suggest a CR endpoint for infants and a separate CR endpoint for children. The same clarification is made to the secondary endpoint for CR, complete remission

without platelet recovery (CRp), complete remission with partial hematologic recovery (CRh), and complete remission with incomplete hematologic recovery (CRi) after consolidation therapy.

- Allow bone marrow to be assessed by aspirate or biopsy or flow if morphology is not available, and permit bone marrows that are performed as part of routine medical care to be used for central laboratory minimal residual disease (MRD) assessment
- In the schedule of activities, replace the line for adverse events, serious adverse events, and concomitant therapies review with "X" to prevent any confusion that these will be collected, at a minimum, from screening through safety follow up. No change is made to the timing of these activities.
- Corrections to schedule of activities tables: added row for "other extramedullary disease assessment" and removed day 10 hematology, which was listed in error, from Table 20 (consolidation therapy for subjects less than 12 months of age)
- Remove exclusion criteria 212 and 213. These required a 3-month window after previous proteasome inhibitor therapy, and a 2-month window after previous VXLD (or similar). These exclusions were not present in the phase 1 portion of the protocol, their removal was requested by investigators, and is consistent with guidance to remove time-based washout periods from clinical trials eligibility (Harvey et al, 2021).
- Correct inclusion criterion 113 so eligibility requires less than 5% blasts
- Extend window allowed to make up missed doses from +1 day to +3 days
- Allow alternate dosing or formulation of L-asparaginase in accordance with local standard of care
- Allow substitution of intrathecal regimens based on local practice
- Recommendation to collect medical history and surgical history 30 days prior to signing the ICF is removed to allow collection of full ALL medical history
- Update treatment response definition in alignment with National Comprehensive Cancer Network guidelines (2022) and Shallis et al, 2021, consistency with Study 20180065, and Amgen endpoint guide for leukemia
- Clarify details of the independent Data Monitoring Committee and independent Biostatistics Group, and remove requirement for every 3-month Steering Committee meetings
- Update the covariates for subgroup analyses, and specify the categories into the SAP
- To reduce confusion, the phase 1 pregnancy and lactation notification forms are removed with references to the respective forms to use for phase 2
- Safety reporting language updated per new Amgen protocol template updates
- Revisions made for internal consistency of document (eg, number of allowed screen fails in Section 24.1.1 revised to align with Section 20.4; male contraception time revised in Section 22.1.6.15.3, Male Subjects to align with exclusion criteria)
- Update investigator list on the cover page
- Typographical and formatting issues were corrected throughout the document.

References

Harvey RD, Mileham KF, Vishal Bhatnagar V, et al. Modernizing clinical trial eligibility criteria: recommendations of the ASCO-Friends of Cancer Research washout period and concomitant medication work group. *Clin Cancer Res*. 2021;27:2400-2407.

National Comprehensive Cancer Network. Acute Lymphoblastic Leukemia v1.2022. April 4, 2022.

Shallis RM, Pollyea DA, Zeidan AM. The complete story of less than complete responses: The evolution and application of acute myeloid leukemia clinical responses. *Blood Reviews*. 2021;48:1-10.

Amendment 10

Protocol Title: Phase 1b/2 Study of Carfilzomib in Combination With Induction Chemotherapy in Children With Relapsed or Refractory Acute Lymphoblastic Leukemia

Amgen Protocol Number (Carfilzomib for Injection) 20140106

EudraCT Number 2014-001633-84

NCT Number: 02303821

Amendment Date: 03 August 2021

Rationale:

This protocol is being amended to:

- Remove the pharmacogenetic biomarkers from the exploratory objectives in phase 2.
- Update inclusion criterion #114 to allow subjects who received blinatumomab for treatment of MRD positive disease during first remission or for primary induction failure to achieve a first remission.
- Update exclusion criterion #221 to require discussion with Amgen medical monitor for subjects with less than 3 antibody half-lives since the last dose of monoclonal antibody.
- Add exclusion criterion for known allergy to captisol in phase 2 of the study.
- Add assessments for pancreatic function tests in the Schedule of Activities for phase 2.
- Add assessments for echocardiograms in the Schedule of Activities for phase 2.
- Update treatment of central nervous system-positive subjects to allow alternatives to hydrocortisone substitutions per local standard practice.
- Clarify instructions for lumbar puncture.
- Clarify information collected during long-term follow-up.
- Change day 29 to day 28 in the Schedule of Activities for dose regimen for consolidation therapy in subjects aged less than 12 months at screening.
- Update the reasons for early removal for protocol-required investigational product(s) or procedural assessments.
- Update allowance for rescreening from 1 time to 3 times.
- Add the use of asparaginase erwinia chrysanthemi recombinant (RYLAZE) as a replacement for polyethylene glycol asparaginase or Erwinia asparaginase in regions where approved and available for subjects less than 12 months of age at screening receiving Berlin-Frankfurt-Munster consolidation therapy.
- Administrative, typographical, and formatting changes were made throughout the protocol.

This amendment only applies to the ongoing phase 2 part of the study.

Amendment 9

Protocol Title: Phase 1b/2 Study of Carfilzomib in Combination With Induction Chemotherapy in Children With Relapsed or Refractory Acute Lymphoblastic Leukemia

Amgen Protocol Number 20140106 (formerly CFZ008)

Amendment Date: 04 February 2021

Rationale:

The 20140106 study protocol has been amended as follows:

- The recommended phase 2 dose of 20/56 mg/m^2 carfilzomib identified from phase 1 by the Cohort Safety Review Committee was added.
- Protocol-approved substitutions with dose equivalents were specified for components of VXLD or intrathecal chemotherapy for regions where these components are not available to allow enrollment globally while ensuring comparability of backbone therapy.
- The omission of components of VXLD treatment (eg, anthracycline) under certain conditions or steroid from intrathecal chemotherapy is allowed to be consistent with current clinical practice or local standard of care.
- For subjects $\geq$ 12 months, the dose of daunorubicin during induction was changed from 25 mg/m^2 for 4 doses to 60 mg/m^2 and the dosing frequency was decreased from 4 times to once per cycle (reduced total dose from 100 to 60 mg/m^2). This change is intended to reduce toxicity of the VXLD backbone by both reducing the total daunorubicin dose and to move it earlier in regimen to allow bone marrow function more time to recover. The change matches the design for daunorubicin used with the VPLD backbone in similar patients in COG Study AALL01P2 and Study AALL07P1 (VPLD + bortezomib).
- The rationale for changes to the VXLD regimen in the phase 2 versus phase 1 portions of the study was added.
- Vindesine was removed as an acceptable replacement for vincristine because no planned country/region is expected to require this substitution.
- The discontinuation of asparaginase is allowed if Erwinia asparaginase is not available or desensitization procedure for asparaginase.
- Details on non-investigational products and other protocol-required therapies were added to the phase 2 portion of the study for clarity.
- The recommended dosing of trimethoprim sulfamethoxazole was added along with suggested alternatives for contraindication or significant concerns of bone marrow suppression, with a requirement to include the rationale for the use of an alternative agent in the case report form.

- Clarification was added that adjustment of the carfilzomib dose is required for certain toxicities.
- Dose modification guidelines, including adding guidance for progressive multifocal leukoencephalopathy and resuming carfilzomib with controlled hepatitis B reactivation, were aligned with those of the carfilzomib program for consistency across studies.
- Supportive care requirements and guidelines were updated and guidelines for mucositis was added based on the recommendations of the steering committee.
- The most impactful difference in patient population between phase 1 and phase 2 was clarified.
- A correction was made to the inclusion criterion that adequate cardiac function is defined as shortening fraction of $\geq$ 30% not $>$ 30%.
- A correction was made to the inclusion criterion that life expectancy must be $>$ 6 weeks not $\geq$ 6 weeks.
- Clarification was added to the exclusion criterion that subjects should be excluded for intolerance, hypersensitivity, or inability to receive any of the chemotherapy components of the VXLD regimen (or acceptable substitutes as defined in the protocol).
- Corrections were made to the exclusion criteria that subjects should refrain from becoming pregnant or breastfeeding and must use contraception for 6 months after the last dose of any study treatment or for 12 months after the last dose of cyclophosphamide if used.
- A recommendation was added that oral hormonal contraception not be used during PEG- or Erwinia asparaginase treatment due to a potential interaction.
- Collection of serious adverse events was extended through long-term follow-up for compliance with clinical trial guidance.
- A requirement for cytomegalovirus (CMV) polymerase chain reaction (PCR) testing at screening was added for subjects with prior transplant. CMV PCR testing at screening was added to the schedule of assessments and analyte listing to clarify the required testing for these subjects and those who are CMV positive, and to further clarify that CMV testing is recommended for all subjects.
- Clarification was added to the schedule of assessments that subjects with symptoms of congestive heart failure during or after completion of induction therapy should have an echocardiogram before optional consolidation.
- The timing of hematology collection in induction and consolidation for infants was corrected to day 36 (not day 35).
- Clarification was added to the schedule of assessments the clinical chemistry parameters that are required beyond a standard metabolic panel.
- A correction was made to remove cholesterol, HDL, LDL, and triglycerides from the analyte listing because they are not required for any exclusion criteria or monitoring.
- Clarification was added that calculated creatinine clearance or glomerular filtration rate is required at screening.
- Segmented neutrophils was added to the analyte listing to allow for calculation of total neutrophils.

- The requirement for unstained slides of bone marrow aspirate and peripheral blood were removed.
- Clarification was added that chest imaging is only required for subjects with a mass present at screening.
- [redacted] blood sample collection was added at 60 minutes after the end of carfilzomib infusion on day 1 of induction to better monitor proteasome inhibition.
- [redacted] pharmacokinetic blood sample collection were added during consolidation to allow comparison between induction and consolidation
- The dosing schedule of study treatments was separated from the schedule of assessments for consistency with phase 1 and other cooperative protocols.
- Clarification was added that subjects may be discontinued from study treatment due to death and for those determined to be ineligible for the study.
- The objectives, endpoints, and analysis sets of the phase 2 portion were aligned with the statistical analysis plan (SAP).
- Phase 2 endpoints were clarified (eg, removal of 'full' from complete response because it has no meaning). None of the edits change the endpoints themselves.
- The treatment response definitions were updated per more recent United States Food and Drug Administration (US FDA) requirements and a definition for non-evaluable was added.
- The definition of induction death was clarified with respect to the timing of response evaluation.
- Clarification was added that assessment of response is central review of stained slides of bone marrow aspirate, peripheral blood, and minimal residual disease (MRD) by next generation sequencing (NGS) and local assessment of sites of extramedullary disease and MRD by flow cytometry and/or PCR or NGS if available
- The missing baseline covariates imputation, sample size determination, and statistical analysis sections were updated to be consistent with SAP version 2.0, dated 19 November 2020 which was amended based on the feedback from the US FDA.
- Statistical comparison between experimental arm and external control arm of duration of response was removed and only descriptive statistics will be summarized because it will be analyzed only on responders in the Primary Analysis Set.
- Subgroup analyses for subjects who had anthracycline omitted from VXLD induction were added. Relapse time from prior transplant, number of prior relapses, and duration of most immediate prior remission subgroups were aligned with SAP.
- Clarification was added that a sensitivity analysis will include any covariates still imbalanced after propensity score analysis.
- The planned analyses for echocardiograms were added.
- Details about the role of the independent biostatisticians who will support the futility efficacy analysis for Data Monitoring Committee (DMC) were added.
- The investigators on the cover page were updated to reflect the anticipated involvement in the phase 2 portion of the study.
- The anticipated number of sites participating in phase 2 was added.

- A reference was added in the DMC section of the phase 1 protocol to the corresponding section for phase 2 to clarify the different roles of the DMC across phases.
- Typographical and formatting issues were corrected throughout the document.

Amendment 8

Protocol Title: Phase 1b/2 Study of Carfilzomib in Combination With Induction Chemotherapy in Children With Relapsed or Refractory Acute Lymphoblastic Leukemia

Amgen Protocol Number 20140106

Amendment Date: 13 August 2020

Rationale:

The 20140106 study protocol has been amended as follows:

- Addition of the phase 2 part to the existing phase 1 study to allow currently participating sites to seamlessly continue to enroll subjects without a break in availability of this therapy for subjects that may benefit from carfilzomib combined with vincristine, dexamethasone, PEG-asparaginase, and daunorubicin (VXLD).
- The primary objective of the phase 1 part of the study has been amended to clarify that in addition to determining the maximum tolerated dose, the objective is also to recommend a phase 2 dose of carfilzomib with induction therapy.
- Typographical and formatting changes have been made throughout the document.

Amendment 7

Protocol Title: Phase 1b Study of Carfilzomib in Combination With Induction Chemotherapy in Children With Relapsed or Refractory Acute Lymphoblastic Leukemia

Amgen Protocol Number carfilzomib 20160104 (formerly CFZ008)

Amendment Date: 19 September 2019

Rationale:

The protocol is amended to:

- To add hepatitis B testing at screening for all subjects and at the safety follow up for subjects with positive hepatitis B serology at screening or past history of HBV infection. Subjects with hepatitis B infection with positive hepatitis B DNA are excluded from the study. In addition, guidance was provided for the monitoring and management of HBV infections.
- To allow enrollment of subjects with first refractory bone marrow relapse occurring any time after original diagnosis after achieving a CR (ie, $\geq$ 1 failed attempt to induce a second remission) in the study.
- To indicate that prior therapy with inotuzumab within 36 days (3 antibody half-lives), rather than 30 days, is exclusionary.
- To indicate that next generation sequencing will be used to assess MRD status and lymphoblasts at the end of the Induction Cycle.
- To indicate that the degree of proteasome inhibition will only be assayed in whole blood.
- To clarify that subjects should be in a rested and clam state before blood pressure measurements but are not required to be supine.
- To clarify the reporting requirements for AEs that are laboratory findings that do not result in a clinical action or alter treatment.
- To clarify that for the Cohort Safety Review Committee and the Data Monitoring Committee as-is snapshots will be used for the analyses.
- To clarify that for the final analyses the database will be cleaned, processed and a locked database used in the analysis.
- Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document.

APPENDIX K SUMMARY OF CHANGES

Amendment 6

Protocol Title: Phase 1b Study of Carfilzomib in Combination With Induction Chemotherapy in Children With Relapsed or Refractory Acute Lymphoblastic Leukemia

Amgen Protocol Number 20140106 (formerly CFZ008)

Amendment Date: 24 October 2018

Rationale:

The protocol is amended to:

- Modify the stopping criteria for the Bayesian algorithm

  Rationale: Changes to language on how the Bayesian output will be used to determine the maximum tolerated dose in order to trigger the end of the study.

- Update the cohort safety review committee language.

  Rationale: Update increases the discretion of the cohort safety review committee to recommend the maximum tolerated dose.

- Add 2 additional dose levels in dose escalation 2

  Rationale: Accumulating pharmacokinetic data in children indicates drug exposure was approximately 40% lower than that of adults at the same dose and schedule; therefore, current dose escalation plan updated to include 2 higher dose levels.

- Minor modifications to the definition of dose limiting toxicities that are based on biochemical adverse events without clinical manifestations

- Administrative updates, editorial changes, and style and formatting revisions have been made to improve clarity and consistency throughout the document. Significant changes are described in the table below. Detailed, changed text is displayed for first major occurrence only. Changes in sections of the protocol body were also made in the protocol synopsis and elsewhere in the document, as applicable. Added text is presented in bold format.

APPENDIX K SUMMARY OF CHANGES

Amendment 5

Protocol Title: Phase 1b Study of Carfilzomib in Combination With Induction Chemotherapy in Children With Relapsed or Refractory Acute Lymphoblastic Leukemia

Amgen Protocol Number 20140106 (formerly CFZ008)

Amendment Date: 11 September 2017

Rationale:

The protocol is amended to:

- Modify the language for dexamethasone dose instruction in the VXLD regimen from 6 mg/m^2 twice daily to 6 mg/m^2 per day BID – given orally (3 mg/m^2 per dose given twice daily).

  Rationale: Update the language describing required dexamethasone dosing instructions to ensure clarity and remove ambiguity.

- Update the posterior reversible encephalopathy syndrome (PRES) language.

  Rationale: Update PRES language to ensure alignment between study protocol and the carfilzomib Investigator Brochure v17.1.

- Update PRES management recommendation with a no "re-challenge requirement".

  Rationale: Prohibit reintroduction of carfilzomib if PRES is identified in a subject at the request of the Global Safety Team (GST).

- Administrative updates, editorial changes, and style and formatting revisions have been made to improve clarity and consistency throughout the document. Significant changes are described in the table below. Detailed, changed text is displayed for first major occurrence only. Changes in sections of the protocol body were also made in the protocol synopsis and elsewhere in the document, as applicable. Added text is presented in bold format.

APPENDIX K SUMMARY OF CHANGES

Amendment 4

Protocol Title: Phase 1b Study of Carfilzomib in Combination with Induction Chemotherapy in Children with Relapsed or Refractory Acute Lymphoblastic Leukemia

Amgen Protocol Number 20140106 (formerly CFZ008)

Amendment Date: 22 February 2017

Rationale:

The protocol is amended to:

- Revise inclusion criteria regarding hepatic function

  Rationale: Provide clarity that subjects with hyperbilirubinemia due to Gilbert syndrome are only eligible if they have a direct bilirubin ≤ 1.5 x institutional upper limit of normal.

- Modify carfilzomib infusion time from "approximately 30 minutes" to "30 ± 5 minutes"

  Rationale: Provide clarity on the infusion time ensuring all subjects are exposed to the same range of IV infusion time.

- Add language within the Induction Cycle describing the dose level lists with the carfilzomib dose for each dose escalation and specify that during Dose Escalation 2, subjects will receive 20 mg/m^2 of carfilzomib on Day 1 of the Induction Cycle.

  Rationale: This language was erroneously omitted during Amendment 3.

- Update Study 20140106 Induction Cycle Dose Escalation 2 (VXLD) road map with actual dose administered placeholders to match the VXLD backbone.

  Rationale: Dexamethasone, vincristine, and PEG-asparaginase administration placeholders were not correctly placed within the appropriate study day.

- Administrative updates, editorial changes, and style and formatting revisions have been made to improve clarity and consistency throughout the document. Significant changes are described in the table below. Detailed, changed text is displayed for first major occurrence only. Changes in sections of the protocol body were also made in the protocol synopsis and elsewhere in the document, as applicable. Deletions of text are presented in strikethrough format. Added text is presented in bold format.

APPENDIX K SUMMARY OF CHANGES

Amendment 3

Protocol Title: Phase 1b Study of Carfilzomib in Combination with Induction Chemotherapy in Children with Relapsed or Refractory Acute Lymphoblastic Leukemia

Amgen Protocol Number Carfilzomib for Injection 20140106 (formerly CFZ008)

Amendment Date: 20 October 2016

Rationale:

The protocol is amended to:

- Add a second dose escalation portion to evaluate carfilzomib with a different chemotherapy backbone (VXLD) of vincristine, dexamethasone, PEG-asparaginase, and daunorubicin

  Rationale: Toxicity related to the R3 induction chemotherapy backbone of dexamethasone, mitoxantrone, PEG-asparaginase, and vincristine is suspected to have limited the ability to dose escalate carfilzomib. A second dose escalation using the less toxic VXLD backbone is being added to the protocol to ensure the optimal dose of carfilzomib is selected before moving on to a Phase 2 study.

- Remove the Phase 2 portion of the study

  Rationale: The Phase 2 portion of the study will instead be conducted with a stand-alone protocol treating subjects at the defined MTD.

- Revise eligibility criteria to
  - Include enrollment of subjects aged 21 years or younger at the time of initial ALL diagnosis and limiting enrollment to those aged > 1 year at the time of study treatment initiation
  - Include the enrollment of subjects with any first relapse of T-ALL, removing the limitation to those with an early relapse

  - Modify definition of adequate liver function
  - Specify grade of pancreatitis as an exclusion criterion
  - Clarify evidence for bacteria or fungal infection
  - Clarify antineoplastic agents that are included in prior therapy restrictions
- Clarify the target number of subjects to be enrolled in each age group
- Change requirement for medical monitor approval with requirement to contact medical monitor
- Remove the requirement for bone marrow biopsy during screening
- Revise Section 8.4 (Dose Modification Guidelines) to
  - Add text clarifying that the carfilzomib dose modification guidelines also apply to the Optional Consolidation Cycle
  - Add dose modification guidelines for daunorubicin
- Add Section 8.6 (Product Complaints)
- Revise Section 9 (Supportive Care Requirements and Guidelines) to
  - Clarify that fungal prophylaxis must be provided during periods of neutropenia
  - Correct definition for fever and neutropenia
  - Update Section 9.14 (Contraception)
- Update Section 12.6 (Pregnancy and Lactation Reporting)
- Add guidelines for taking temperature and blood pressure of subjects
- Add Section 15.7 (Publication Policy)
- Update Section 3 (Background Information)
- Make minor text clarifications, additions, and edits throughout the protocol

APPENDIX H SUMMARY OF CHANGES

Administrative updates, editorial changes, and style and formatting revisions have been made to improve clarity and consistency throughout the document. Significant changes are described in the table below.

Significant changes from the Protocol Amendment 1 to Amendment 2 are:

- Added details of MRD specimen collection, including the type of specimen to be submitted or the timing of the specimen collection
- Added detailed information regarding timing of [redacted] specimen collection
- Corrected inconsistencies within the protocol and between the protocol and the laboratory manual regarding the proper day for collection of blood or saliva to serve as a source of normal (non-tumor) DNA from subjects who have consented to the optional genomic studies
- Removed ≥ Grade 3 peripheral neuropathy or neuropathic pain from the definition of dose limiting toxicity, due to its strong association with vincristine and rare association with carfilzomib
- Corrected the dose modification of vincristine in the setting of constipation, ileus, or typhlitus to reflect modification at ≥ Grade 3, rather than > Grade 3
- Added information about PRES and the required dose modification of carfilzomib when PRES is suspected
- Updated the options for pregnancy testing during screening to include a urine pregnancy test, to include a urine pregnancy test, which is less invasive and more readily available at pediatric facilities

- Increased the duration of required contraception to incorporate the best practices for all drugs in the treatment regimen
- Modified the definition of permanent sterilization and revised the list of highly effective methods of contraception, to be consistent with recent guidance
- Added language to allow for higher total bilirubin level at screening, for subjects with a diagnosis of Gilbert syndrome
- Added language to clarify that the restricted use of antineoplastic agents prior to enrollment only applies to the use of agents with therapeutic intent

Administrative updates, editorial changes, and style and formatting revisions have been made to improve clarity and consistency throughout the document. Significant changes are described in the table below. Detailed, changed text is displayed for first major occurrence only. Changes in sections of the protocol body were also made in the protocol synopsis and elsewhere in the document, as applicable. Deletions of text are presented in strikethrough format. Added text is presented in bold format.

APPENDIX H: SUMMARY OF CHANGES

Administrative updates, editorial changes, and style and formatting revisions have been made to improve clarity and consistency throughout the document. Significant changes are described in the table below.

Significant changes from the Original Protocol to Amendment 1 are:

- Added PK sample collection times of 2 and 4 hours after the end of carfilzomib infusion
- Germline DNA collection time moved to the end of Induction
- [redacted]