Clinical trial results:
Phase 1b/2 Study of Carfilzomib in Combination With Induction Chemotherapy in Children with Relapsed or Refractory Acute Lymphoblastic Leukemia

Summary

EudraCT number	2014-001633-84
Trial protocol	IT GB ES FR AT DK NL SE GR PL PT BG NO CZ RO
Global end of trial date	28 June 2024

Results information

Result version number	v1
This version publication date	26 December 2024
First version publication date	26 December 2024

Trial information

Trial identification

Sponsor protocol code	CFZ008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02303821
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, United States,
Public contact	Amgen (EUROPE) GmbH, IHQ Medical Info-Clinical Trials, MedInfoInternational@amgen.com
Scientific contact	Amgen (EUROPE) GmbH, IHQ Medical Info-Clinical Trials, MedInfoInternational@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001806-PIP04-19
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 June 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to compare the rate of complete remission (CR) of relapsed or refractory pediatric ALL to treatment with carfilzomib with vincristine, dexamethasone, PEG-asparaginase, and daunorubicin (CFZVXLD) at the end of induction therapy to an appropriate external control selected from an observational study (Amgen 20180065).

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 September 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Brazil: 24
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 6
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Russian Federation: 3

Country: Number of subjects enrolled	Saudi Arabia: 1
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Türkiye: 14
Worldwide total number of subjects	105
EEA total number of subjects	36

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	4
Children (2-11 years)	68
Adolescents (12-17 years)	26
Adults (18-64 years)	7
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with relapsed or refractory acute lymphoblastic leukemia were recruited for the Phase 2 across 106 centers in different countries. Phase 1 enrollment started February 2015; Phase 2 enrollment started from September 2021 and the study completed in June 2024.

Pre-assignment

Screening details:

Participants were screened for up to 7 days and treated with with VXLD (vincristine, polyethylene glycol [PEG] asparaginase, daunorubicin, dexamethasone) plus carfilzomib during a 28-day induction. One B-cell participant did not receive carfilzomib and was excluded from the efficacy analysis. Participants were followed for up to 2 years.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	B-cell

Arm description:

Eligible participants with relapsed or refractory acute lymphoblastic leukemia (B-cell) were treated with VXLD plus carfilzomib for 1 cycle (induction), followed by assessment of treatment response. Participants who did not show progression during induction underwent a bone marrow and extramedullary disease evaluation after completion of induction therapy. Participants without disease progression after induction could at the investigator’s discretion, be treated with 1 28-day consolidation cycle of Children’s Oncology group-modified Berlin-Frankfurt-Munster (BFM) therapy (cyclophosphamide, cytarabine, 6-mercaptopurine, PEG-asparaginase, vincristine), and intrathecal (IT) therapy plus carfilzomib.

Arm type	Experimental
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous (IV) infusion

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV Infusion

Investigational medicinal product name	PEG-asparaginase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV Infusion

Investigational medicinal product name	Daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV Infusion

Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV Infusion

Arm title	T-cell

Arm description:

Eligible participants with relapsed or refractory acute lymphoblastic leukemia (T-cell) were treated with VXLD plus carfilzomib for 1 cycle (induction), followed by assessment of treatment response. Participants who did not show progression during induction underwent a bone marrow and extramedullary disease evaluation after completion of induction therapy. Participants without disease progression after induction could at the investigator’s discretion, be treated with 1 28-day consolidation cycle of BFM therapy (cyclophosphamide, cytarabine, 6-mercaptopurine, PEG-asparaginase, vincristine), and IT therapy plus carfilzomib.

Arm type	Experimental
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV infusion

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV Infusion

Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV Infusion

Investigational medicinal product name	Daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV Infusion

Investigational medicinal product name	PEG-asparaginase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV Infusion

Number of subjects in period 1	B-cell	T-cell
Started	61	44
Received IP in induction therapy	61	44
Received IP in consolidation therapy	25	20
Completed	19	13
Not completed	42	31
Adverse event, serious fatal	41	29
Consent withdrawn by subject	-	2
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	B-cell

Reporting group description:

Eligible participants with relapsed or refractory acute lymphoblastic leukemia (B-cell) were treated with VXLD plus carfilzomib for 1 cycle (induction), followed by assessment of treatment response. Participants who did not show progression during induction underwent a bone marrow and extramedullary disease evaluation after completion of induction therapy. Participants without disease progression after induction could at the investigator's discretion, be treated with 1 28-day consolidation cycle of Children's Oncology group-modified Berlin-Frankfurt-Munster (BFM) therapy (cyclophosphamide, cytarabine, 6-mercaptopurine, PEG-asparaginase, vincristine), and intrathecal (IT) therapy plus carfilzomib.

Reporting group title	T-cell

Reporting group description:

Eligible participants with relapsed or refractory acute lymphoblastic leukemia (T-cell) were treated with VXLD plus carfilzomib for 1 cycle (induction), followed by assessment of treatment response. Participants who did not show progression during induction underwent a bone marrow and extramedullary disease evaluation after completion of induction therapy. Participants without disease progression after induction could at the investigator's discretion, be treated with 1 28-day consolidation cycle of BFM therapy (cyclophosphamide, cytarabine, 6-mercaptopurine, PEG-asparaginase, vincristine), and IT therapy plus carfilzomib.

Reporting group values	B-cell	T-cell	Total
Number of subjects	61	44	105
Age Categorical Units: Subjects			
< 1 month	0	0	0
1 month - <= 17 years	57	41	98
> 17 years	4	3	7
Age Continuous Units: years			
arithmetic mean	9.04	10.59	
standard deviation	± 5.15	± 4.42	-
Gender Categorical Units: Subjects			
Female	19	5	24
Male	42	39	81
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	28	11	39
Not Hispanic or Latino	33	33	66
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	2	2	4
Asian	9	6	15
Black or African American	2	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
White	38	33	71
Other	9	1	10
Multiple	1	0	1

Unknown	0	0	0

End points

End points reporting groups

Reporting group title	B-cell

Reporting group description:

Eligible participants with relapsed or refractory acute lymphoblastic leukemia (B-cell) were treated with VXLD plus carfilzomib for 1 cycle (induction), followed by assessment of treatment response. Participants who did not show progression during induction underwent a bone marrow and extramedullary disease evaluation after completion of induction therapy. Participants without disease progression after induction could at the investigator's discretion, be treated with 1 28-day consolidation cycle of Children's Oncology group-modified Berlin-Frankfurt-Munster (BFM) therapy (cyclophosphamide, cytarabine, 6-mercaptopurine, PEG-asparaginase, vincristine), and intrathecal (IT) therapy plus carfilzomib.

Reporting group title	T-cell

Reporting group description:

Eligible participants with relapsed or refractory acute lymphoblastic leukemia (T-cell) were treated with VXLD plus carfilzomib for 1 cycle (induction), followed by assessment of treatment response. Participants who did not show progression during induction underwent a bone marrow and extramedullary disease evaluation after completion of induction therapy. Participants without disease progression after induction could at the investigator's discretion, be treated with 1 28-day consolidation cycle of BFM therapy (cyclophosphamide, cytarabine, 6-mercaptopurine, PEG-asparaginase, vincristine), and IT therapy plus carfilzomib.

Subject analysis set title	Carfilzomib - Day 8 Induction Cycle (PK Analysis Set)
Subject analysis set type	Full analysis

Subject analysis set description:

Eligible participants with relapsed or refractory acute lymphoblastic leukemia who had PK assessments on Day 8 of the induction cycle.

Subject analysis set title	Carfilzomib - Day 1 Consolidation Cycle (PK Analysis Set)
Subject analysis set type	Full analysis

Subject analysis set description:

Eligible participants with relapsed or refractory acute lymphoblastic leukemia who had PK assessments on Day 1 of the consolidation cycle.

Primary: Complete Remission (CR) After Induction Therapy

End point title	Complete Remission (CR) After Induction Therapy

End point description:

CR was defined as:
a. 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.
b. Recovery of peripheral counts:
- Absolute neutrophil count (ANC) greater than or equal to 1000/µL
- Platelet count greater than or equal to 100000/µL.
Data was adjusted as inverse probability of treatment weight (IPTW) for the average treatment effect of the treated (IPTW-ATT).

Participants enrolled in 20140106, in the Primary Analysis Set (PAS), who received at least 1 dose of carfilzomib.

End point type	Primary

End point timeframe:

Up to Day 50 (28-day cycle of induction therapy + recovery window from Day 29 to Day 45 [up to Day 50 for infants])

End point values	B-cell	T-cell		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	44		
Units: Percentage of Participants				
number (confidence interval 95%)	14.8 (5.9 to 23.7)	13.6 (3.5 to 23.8)		

Statistical analyses

Statistical analysis title	Participants Achieving CR - 20140106 vs control

Statistical analysis description:

The primary objective of this endpoint was to compare the percentage of participants achieving CR after the end of induction therapy in study 20140106 with the percentage of participants achieving CR in an external control arm selected from an observational study (Amgen 20180065).

Comparison groups	T-cell v B-cell
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 99999 [2]
Method	External comparison

Notes:

[1] - In the external control arm, 7.8% of B-Cell participants (95% confidence interval [CI]: 1.0%, 14.7%) achieved CR, with a treatment difference odds ratio of 2.04 (95% CI: 0.54, 7.66). For T-Cell participants, 9.1% (95% CI: 0.7%, 17.5%) achieved CR, with an odds ratio of 1.58 (95% CI: 0.47, 5.31).
[2] - Value of "99999" indicates no P-value.

Secondary: Number of Participants who Experienced Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Participants who Experienced Treatment-emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical study participant, regardless of a causal relationship with the study treatment. TEAEs are AEs occurring after the start of study treatment and up to the end of the study or 30 days after the last study treatment, whichever is earlier. Clinically significant changes in vital signs, electrocardiograms, and clinical lab tests after treatment were recorded as TEAEs. Treatment-related adverse events (TRAEs) are TEAEs considered related to at least one study drug by the investigator, including those with unknown relationship. A serious AE (SAE) is defined as any untoward event that results in death, is life-threatening, requires/prolongs hospitalization, results in disability/incapacity, a congenital anomaly, or is another medically important serious event.
Safety Analysis Set: All participants enrolled in study 20140106 who received at least 1 dose of carfilzomib.

End point type	Secondary

End point timeframe:

From first dose of carfilzomib up to 30 days after the last dose of study treatment; median duration of carfilzomib treatment was 16 days.

End point values	B-cell	T-cell		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	44		
Units: Participants				
TEAEs	61	44		
SAEs	44	31		
Fatal TEAEs	15	3		
TRAEs	50	39		
Serious TRAEs	25	24		
Fatal TRAEs	5	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants CR with Incomplete Hematologic Recovery (CRi) After Induction Therapy or Better Remission Status

End point title	Percentage of Participants CR with Incomplete Hematologic Recovery (CRi) After Induction Therapy or Better Remission Status

End point description:

CR was defined as: a. Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease. b. Recovery of peripheral counts: - ANC ≥ 1000/µL - Platelet count ≥ 100 000/µL.

CRi was defined as:
a. Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease
b. ANC and platelet counts not fulfilling criteria for CR with partial hematologic recovery (CRh), CR without platelet recovery (CRp), or CR.

CRp was defined as:
a. Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease
b. Recovery of peripheral counts:
i. ANC ≥ 1000/µL
ii. Platelet count < 100 000/µL.

CRh was defined as:
a. Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease
b. Recovery of peripheral counts:
i. ANC ≥ 500/µL but < 1000/µL
ii. Platelet count ≥ 50 000/µL but < 100 000/µL.
Data was IPTW adjusted.

End point type	Secondary

End point timeframe:

Up to Day 50 (28-day cycle of induction therapy + recovery window from Day 29 to Day 45 [up to Day 50 for infants])

End point values	B-cell	T-cell		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61[3]	44[4]		
Units: Percentage of Participants				
number (confidence interval 95%)	42.6 (30.2 to 55.0)	27.3 (14.1 to 40.4)		

Notes:

[3] - Participants enrolled in 20140106, in the PAS, who received at least 1 dose of carfilzomib.

[4] - Participants enrolled in 20140106, in the PAS, who received at least 1 dose of carfilzomib.

Statistical analyses

Statistical analysis title	rate of CRi - 20140106 vs control

Statistical analysis description:

The objective of this endpoint was to compare the rate of CRi or better status against an external control arm selected from an observational study (Amgen 20180065).

Comparison groups	B-cell v T-cell
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 99999 [6]
Method	External comparison

Notes:

[5] - The rate of CRi or better status in the external control arm was 26.3% (95% CI: 15.1, 37.5) for B-Cell participants with treatment difference odds ratio of 2.082% (95% CI: 0.968, 4.477). For T-Cell participants the rate of CRi or better status was 18.6 (95% CI: 7.1, 30.0) with treatment difference odds ratio of 1.646 (95% CI: 0.639. 4.245).

[6] - Value of "99999" indicates no P-value.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as time from initiation of therapy until death from any cause. Participants enrolled in 20140106, in the PAS, who received at least 1 dose of carfilzomib. Medians were estimated using the KM method.

Data was IPTW adjusted.

End point type	Secondary

End point timeframe:

Up to approximately 2 years

End point values	B-cell	T-cell		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	44		
Units: Months				
median (confidence interval 95%)	5.23 (2.93 to 9.24)	4.51 (3.49 to 9.18)		

Statistical analyses

Statistical analysis title	OS 20140106 vs control

Statistical analysis description:

The objective of this endpoint was to compare the OS in study 20140106 with OS in an external control arm selected from an observational study (Amgen 20180065).

Comparison groups	B-cell v T-cell
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 99999 [8]
Method	External comparison

Notes:

[7] - The median OS in months for the B-Cell participants in the external control arm was 8.59 (95% CI: 5.26, 10.59) with a treatment difference hazard ratio of 1.245 (95% CI: 0.805, 1.927). For the T-Cell participants the median OS in months was 7.04 (95% CI: 7.04, NE) with a treatment difference hazard ratio of 1.040 (95% CI: 0.641, 1.688).

[8] - Value of "99999" indicates no P-value.

Secondary: Event Free Survival (EFS)

End point title	Event Free Survival (EFS)

End point description:

EFS was 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 participants that did not receive consolidation), relapse, or death from any cause. CRi was defined as: a. Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease b. ANC and platelet counts not fulfilling criteria for CRh, CRp, or CR.
Participants enrolled in 20140106, in the PAS, who received at least 1 dose of carfilzomib. Medians were estimated using the Kaplan-Meier (KM) method.

Data was IPTW adjusted.

End point type	Secondary

End point timeframe:

Up to approximately 2 years

End point values	B-cell	T-cell		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	44		
Units: Months				
median (confidence interval 95%)	1.18 (0.95 to 2.24)	1.20 (0.95 to 1.48)		

Statistical analyses

Statistical analysis title	EFS 20140106 vs control

Statistical analysis description:

The objective of this endpoint was to compare EFS in study 20140106 with EFS in an external control arm selected from an observational study (Amgen 20180065).

Comparison groups	B-cell v T-cell

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 99999 [10]
Method	External comparison

Notes:

[9] - The median duration in months in the external control arm was 3.62 (95% CI: 1.55, 5.36) for B-cell participants, with a treatment difference hazard ration of 1.435 (95% CI: 0.976, 2.111). For T-Cell participants the median in months was 2.93 (95% CI: 0.95, 5.10) with a treatment difference hazard ratio of 1.404 (95% CI: 0.869, 2.270).

[10] - Value of "99999" indicates no P-value.

Secondary: Duration of Remission (DOR)

End point title	Duration of Remission (DOR)

End point description:

DOR was defined as time from earliest of CR, CRp, CRh, or CRi to relapse or death from any cause. CR was defined as: a. Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease. b. Recovery of peripheral counts: - ANC ≥ 1000/µL - Platelet count ≥ 100 000/µL. CRi was defined as: a. Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease b. ANC and platelet counts not fulfilling criteria for CRh, CRp) or CR. CRp was defined as: a. Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease b. Recovery of peripheral counts: i. ANC ≥ 1000/µL ii. Platelet count < 100 000/µL. CRh was defined as: a. Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease b. Recovery of peripheral counts: i. ANC ≥ 500/µL but less than 1000/µL ii. Platelet count ≥ 50 000/µL but less than 100 000/µL.

End point type	Secondary

End point timeframe:

Up to approximately 2 years

End point values	B-cell	T-cell		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	14[11]		
Units: Months				
median (confidence interval 95%)	7.55 (3.42 to 22.20)	9.01 (2.57 to 99999)		

Notes:

[11] - Value of "99999" indicates that no upper CI was calculated due to few observations.

Statistical analyses

Statistical analysis title	DOR 20140106 vs control

Statistical analysis description:

The DOR in study 20140106 was estimated relative to the DOR in an external control arm selected from an observational study (Amgen 20180065).

Comparison groups	B-cell v T-cell
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 99999 [13]
Method	External Comparison

Notes:

[12] - The median DOR in months in the external control arm was 8.72 (95% CI: 5.07, 32.24) in B-Cell participants. For T-Cell participants the median DOR in months was 5.82 (95% CI: 1.22, 19.80).
[13] - Value of "99999" indicates no P-value.

Secondary: Percentage of Participants Achieving Minimal Residual Disease (MRD) Status of $<10^3$ and $<10^4$ Cells in Participants With CR After Induction Therapy

End point title	Percentage of Participants Achieving Minimal Residual Disease (MRD) Status of $<10^3$ and $<10^4$ Cells in Participants With CR After Induction Therapy

End point description:

MRD was defined as the number of leukemia cells that remained in a participant's body after treatment. MRD was measured with next generation sequencing (NGS).
Induction Safety Analysis Set: All participants who started the induction cycle and received at least 1 dose of carfilzomib during the induction period.

End point type	Secondary

End point timeframe:

Up to Day 50 (28-day cycle of induction therapy + recovery window from Day 29 to Day 45 [up to Day 50 for infants])

End point values	B-cell	T-cell		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	44		
Units: Percentage of Participants				
number (confidence interval 95%)				
Percentage of Participants Achieving MRD $<10^3$	8.2 (2.7 to 18.1)	4.5 (0.6 to 15.5)		
Percentage of Participants Achieving MRD $<10^4$	3.3 (0.4 to 11.3)	4.5 (0.6 to 15.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving MRD Status of $<10^3$ and $<10^4$ Cells in Participants With CRi or Better Status After Induction Therapy

End point title	Percentage of Participants Achieving MRD Status of $<10^3$ and $<10^4$ Cells in Participants With CRi or Better Status After Induction Therapy

End point description:

MRD was defined as the number of leukemia cells that remained in a participant's body after treatment. MRD was measured with NGS. Induction Safety Analysis Set: All participants who started the induction cycle and received at least 1 dose of carfilzomib during the induction period.

End point type	Secondary

End point timeframe:

Up to Day 50 (28-day cycle of induction therapy + recovery window from Day 29 to Day 45 [up to Day 50 for infants])

End point values	B-cell	T-cell		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	44		
Units: Percentage of Participants				
number (confidence interval 95%)				
Percentage of Participants Achieving MRD $<10^3$	18.0 (9.4 to 30.0)	9.1 (2.5 to 21.7)		
Percentage of Participants Achieving MRD $<10^4$	9.8 (3.7 to 20.2)	6.8 (1.4 to 18.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Underwent Stem Cell Transplant or Chimeric Antigen Receptor T-cell (CAR-T) Without Intervening Relapse Following Protocol-Specified Therapy

End point title	Percentage of Participants Who Underwent Stem Cell Transplant or Chimeric Antigen Receptor T-cell (CAR-T) Without Intervening Relapse Following Protocol-Specified Therapy

End point description:

Percentage of participants who successfully underwent stem cell transplant or CAR-T therapy without experiencing a relapse after receiving the protocol-specified treatment.
Safety analysis set: All participants who received at least 1 dose of carfilzomib.

End point type	Secondary

End point timeframe:

Up to approximately 2 years

End point values	B-cell	T-cell		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	44		
Units: Percentage of Participants				
number (confidence interval 95%)	19.7 (10.6 to 31.8)	27.3 (15.0 to 42.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving MRD Status of $<10^3$ and $<10^4$ Cells in Participants With CRi or Better Status After Consolidation Therapy

End point title	Percentage of Participants Achieving MRD Status of $<10^3$ and $<10^4$ Cells in Participants With CRi or Better Status After Consolidation Therapy

End point description:

MRD was defined as the number of leukemia cells that remained in a participant's body after treatment.

MRD was measured with NGS. Consolidation Safety Analysis Set: All participants who started the consolidation cycle and received at least 1 dose of study treatment during the consolidation period.

End point type	Secondary

End point timeframe:

Up to Day 50 (28-day cycle of induction therapy + recovery window from Day 29 to Day 45 [up to Day 50 for infants])

End point values	B-cell	T-cell		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	20		
Units: Percentage of Participants				
number (confidence interval 95%)				
Percentage of Participants Achieving MRD $<10^3$	16.0 (4.5 to 36.1)	20.0 (5.71 to 43.7)		
Percentage of Participants Achieving MRD $<10^4$	16.0 (4.5 to 36.1)	20.0 (5.71 to 43.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With CRi After Consolidation Therapy or Better Remission Status

End point title	Percentage of Participants With CRi After Consolidation Therapy or Better Remission Status

End point description:

CR was defined as: a. Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease. b. Recovery of peripheral counts: - ANC ≥ 1000/µL - Platelet count ≥ 100 000/µL.
CRi was defined as:
a. Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease
b. ANC and platelet counts not fulfilling criteria for CRh, CRp, or CR.

CRp was defined as:
a. Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease
b. Recovery of peripheral counts:
i. ANC ≥ to 1000/µL
ii. Platelet count < 100 000/µL.

CRh was defined as:
a. Attainment of M1 bone marrow status with no evidence of circulating blasts or extramedullary disease
b. Recovery of peripheral counts:
i. ANC ≥ 500/µL but < 1000/µL
ii. Platelet count ≥ 50 000/µL but < 100 000/µL.

Data was IPTW adjusted.

End point type	Secondary

End point timeframe:

Up to Day 50 (28-day cycle of induction therapy + recovery window from Day 29 to Day 45 [up to Day 50 for infants])

End point values	B-cell	T-cell		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[14]	20[15]		
Units: Percentage of Participants				
number (confidence interval 95%)				
Percentage of participants with CRi or better	36.0 (18.0 to 57.5)	50.0 (27.2 to 72.8)		

Notes:

[14] - All participants who started the consolidation cycle.

[15] - All participants who started the consolidation cycle.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Carfilzomib

End point title	Maximum Concentration (Cmax) of Carfilzomib

End point description:

Cmax is the maximum concentration of a drug in the bloodstream after administration. PK analysis set: All participants who received at least 1 dose of carfilzomib, had 1 PK sample collected and a quantifiable number of observations. Per SAP, analysis was not planned to compare T-cell and B-cell.

End point type	Secondary

End point timeframe:

Day 8 of induction cycle (28-days cycle) and Day 1 of consolidation cycle (28-days cycle)

End point values	Carfilzomib - Day 8 Induction Cycle (PK Analysis Set)	Carfilzomib - Day 1 Consolidation Cycle (PK Analysis Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83	34		
Units: ng/mL				
arithmetic mean (standard deviation)	9590 (± 27800)	13800 (± 44200)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time 0 to the Last Quantifiable Timepoint (AUClast) of Carfilzomib

End point title	Area Under the Curve From Time 0 to the Last Quantifiable Timepoint (AUClast) of Carfilzomib

End point description:

AUClast refers to the total exposure of a drug in the body over time, calculated from the time of administration until the last measurable concentration in the blood. PK analysis set: All participants who received at least 1 dose of carfilzomib, had 1 PK sample collected and a quantifiable number of observations. Per SAP, analysis was not planned to compare T-cell and B-cell.

End point type	Secondary

End point timeframe:

Day 8 of induction cycle (28-days cycle) and Day 1 of consolidation cycle (28-days cycle)

End point values	Carfilzomib - Day 8 Induction Cycle (PK Analysis Set)	Carfilzomib - Day 1 Consolidation Cycle (PK Analysis Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	83	34		
Units: hr*ng/mL				
arithmetic mean (standard deviation)	4330 (± 10300)	9410 (± 36200)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time 0 to infinity (AUCinf) of Carfilzomib

End point title	Area Under the Curve From Time 0 to infinity (AUCinf) of Carfilzomib

End point description:

AUCinf represents the total drug exposure over time, extrapolated from the time of administration until the drug is completely eliminated from the body. PK analysis set: All participants who received at least 1 dose of carfilzomib, had 1 PK sample collected and a quantifiable number of observations. Per SAP, analysis was not planned to compare T-cell and B-cell.

End point type	Secondary

End point timeframe:

Day 8 of induction cycle (28-days cycle) and Day 1 of consolidation cycle (28-days cycle)

End point values	Carfilzomib - Day 8 Induction Cycle (PK Analysis Set)	Carfilzomib - Day 1 Consolidation Cycle (PK Analysis Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	23		
Units: hr*ng/mL				
arithmetic mean (standard deviation)	4070 (± 11000)	1200 (± 2480)		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-life (t1/2,z) of Carfilzomib

End point title	Terminal Half-life (t1/2,z) of Carfilzomib

End point description:

T1/2,z refers to the time required for the plasma concentration of a drug to decrease by half during the final phase of elimination from the body. PK analysis set: All participants who received at least 1 dose of carfilzomib, had 1 PK sample collected and a quantifiable number of observations. Per SAP, analysis was not planned to compare T-cell and B-cell.

End point type	Secondary

End point timeframe:

Day 8 of induction cycle (28-days cycle) and Day 1 of consolidation cycle (28-days cycle)

End point values	Carfilzomib - Day 8 Induction Cycle (PK Analysis Set)	Carfilzomib - Day 1 Consolidation Cycle (PK Analysis Set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	23		
Units: hour				
arithmetic mean (standard deviation)	0.371 (± 0.162)	0.332 (± 0.0894)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For deaths, from enrollment up to approximately 2 years. For TEAEs, from first dose of carfilzomib up to 30 days after the last dose of study treatment; median duration of carfilzomib treatment was 16 days.

Adverse event reporting additional description:

All-cause mortality is reported for all participants enrolled/randomized in the study. Serious adverse events and other adverse events are reported for all participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	T-cell

Reporting group description:

Eligible participants with relapsed or refractory acute lymphoblastic leukemia (T-cell) were treated with VXLD plus carfilzomib for 1 cycle (induction), followed by assessment of treatment response. Participants who did not show progression during induction underwent a bone marrow and extramedullary disease evaluation after completion of induction therapy. Participants without disease progression after induction could at the investigator's discretion, be treated with 1 28-day consolidation cycle of BFM therapy (cyclophosphamide, cytarabine, 6-mercaptopurine, PEG-asparaginase, vincristine), and IT therapy plus carfilzomib.

Reporting group title	B-cell

Reporting group description:

Eligible participants with relapsed or refractory acute lymphoblastic leukemia (B-cell) were treated with VXLD plus carfilzomib for 1 cycle (induction), followed by assessment of treatment response. Participants who did not show progression during induction underwent a bone marrow and extramedullary disease evaluation after completion of induction therapy. Participants without disease progression after induction could at the investigator's discretion, be treated with 1 28-day consolidation cycle of BFM therapy (cyclophosphamide, cytarabine, 6-mercaptopurine, PEG-asparaginase, vincristine), and IT therapy plus carfilzomib.

Serious adverse events	T-cell	B-cell	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 44 (70.45%)	44 / 61 (72.13%)	
number of deaths (all causes)	29	41	
number of deaths resulting from adverse events			
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			

subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 44 (2.27%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 44 (6.82%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malaise			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinal disorder			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoxia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary veno-occlusive disease			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary oedema			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Tachypnoea			

subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			

subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Procedural nausea			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Toxic cardiomyopathy			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac dysfunction			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cerebral haemorrhage			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral small vessel ischaemic disease			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Consciousness fluctuating			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Toxic encephalopathy			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	1 / 44 (2.27%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Petit mal epilepsy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	4 / 44 (9.09%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 44 (6.82%)	8 / 61 (13.11%)	
occurrences causally related to treatment / all	4 / 4	7 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 44 (9.09%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	9 / 11	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 44 (2.27%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	3 / 44 (6.82%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperleukocytosis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 44 (2.27%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 44 (0.00%)	3 / 61 (4.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 44 (2.27%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disease			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			

subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	2 / 44 (4.55%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Escherichia sepsis			
subjects affected / exposed	3 / 44 (6.82%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	2 / 3	1 / 3	
deaths causally related to treatment / all	1 / 1	0 / 1	
Encephalitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
COVID-19			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 44 (2.27%)	3 / 61 (4.92%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bacterial sepsis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	2 / 44 (4.55%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alpha haemolytic streptococcal infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungaemia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	0 / 44 (0.00%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			

subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex reactivation			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia			
subjects affected / exposed	2 / 44 (4.55%)	4 / 61 (6.56%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	1 / 44 (2.27%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia klebsiella			

subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pseudomonal sepsis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 44 (0.00%)	4 / 61 (6.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis syndrome			
subjects affected / exposed	1 / 44 (2.27%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Septic shock			
subjects affected / exposed	2 / 44 (4.55%)	9 / 61 (14.75%)	
occurrences causally related to treatment / all	1 / 2	3 / 11	
deaths causally related to treatment / all	0 / 1	0 / 2	
Severe acute respiratory syndrome			
subjects affected / exposed	0 / 44 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 44 (4.55%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			

subjects affected / exposed	1 / 44 (2.27%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	2 / 44 (4.55%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	T-cell	B-cell	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 44 (95.45%)	61 / 61 (100.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 44 (9.09%)	3 / 61 (4.92%)	
occurrences (all)	5	3	
Hypertension			
subjects affected / exposed	13 / 44 (29.55%)	25 / 61 (40.98%)	
occurrences (all)	23	28	
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	4 / 44 (9.09%)	1 / 61 (1.64%)	
occurrences (all)	4	1	
Mucosal inflammation			
subjects affected / exposed	0 / 44 (0.00%)	5 / 61 (8.20%)	
occurrences (all)	0	5	
Pain			
subjects affected / exposed	7 / 44 (15.91%)	3 / 61 (4.92%)	
occurrences (all)	9	3	
Pyrexia			
subjects affected / exposed	23 / 44 (52.27%)	27 / 61 (44.26%)	
occurrences (all)	52	57	
Immune system disorders			

Hypogammaglobulinaemia			
subjects affected / exposed	3 / 44 (6.82%)	0 / 61 (0.00%)	
occurrences (all)	6	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 44 (9.09%)	3 / 61 (4.92%)	
occurrences (all)	4	3	
Dyspnoea			
subjects affected / exposed	4 / 44 (9.09%)	2 / 61 (3.28%)	
occurrences (all)	4	2	
Epistaxis			
subjects affected / exposed	4 / 44 (9.09%)	1 / 61 (1.64%)	
occurrences (all)	5	1	
Pleural effusion			
subjects affected / exposed	3 / 44 (6.82%)	5 / 61 (8.20%)	
occurrences (all)	3	6	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	14 / 44 (31.82%)	21 / 61 (34.43%)	
occurrences (all)	32	46	
Antithrombin III decreased			
subjects affected / exposed	5 / 44 (11.36%)	0 / 61 (0.00%)	
occurrences (all)	7	0	
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 44 (22.73%)	18 / 61 (29.51%)	
occurrences (all)	33	35	
Blood bilirubin increased			
subjects affected / exposed	4 / 44 (9.09%)	6 / 61 (9.84%)	
occurrences (all)	4	12	
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 44 (11.36%)	7 / 61 (11.48%)	
occurrences (all)	8	10	
Neutrophil count decreased			
subjects affected / exposed	4 / 44 (9.09%)	6 / 61 (9.84%)	
occurrences (all)	21	19	

Lymphocyte count decreased			
subjects affected / exposed	0 / 44 (0.00%)	4 / 61 (6.56%)	
occurrences (all)	0	9	
International normalised ratio increased			
subjects affected / exposed	3 / 44 (6.82%)	3 / 61 (4.92%)	
occurrences (all)	3	3	
Platelet count decreased			
subjects affected / exposed	4 / 44 (9.09%)	11 / 61 (18.03%)	
occurrences (all)	33	40	
White blood cell count decreased			
subjects affected / exposed	5 / 44 (11.36%)	11 / 61 (18.03%)	
occurrences (all)	27	36	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 44 (0.00%)	4 / 61 (6.56%)	
occurrences (all)	0	5	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 44 (22.73%)	8 / 61 (13.11%)	
occurrences (all)	15	10	
Neuropathy peripheral			
subjects affected / exposed	3 / 44 (6.82%)	4 / 61 (6.56%)	
occurrences (all)	3	4	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	17 / 44 (38.64%)	24 / 61 (39.34%)	
occurrences (all)	39	46	
Lymphopenia			
subjects affected / exposed	4 / 44 (9.09%)	6 / 61 (9.84%)	
occurrences (all)	18	14	
Leukopenia			
subjects affected / exposed	10 / 44 (22.73%)	12 / 61 (19.67%)	
occurrences (all)	17	19	
Febrile neutropenia			
subjects affected / exposed	11 / 44 (25.00%)	17 / 61 (27.87%)	
occurrences (all)	19	19	

Anaemia			
subjects affected / exposed	23 / 44 (52.27%)	37 / 61 (60.66%)	
occurrences (all)	98	145	
Thrombocytopenia			
subjects affected / exposed	20 / 44 (45.45%)	23 / 61 (37.70%)	
occurrences (all)	49	90	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 44 (20.45%)	13 / 61 (21.31%)	
occurrences (all)	11	18	
Nausea			
subjects affected / exposed	11 / 44 (25.00%)	8 / 61 (13.11%)	
occurrences (all)	19	8	
Oral pain			
subjects affected / exposed	3 / 44 (6.82%)	0 / 61 (0.00%)	
occurrences (all)	3	0	
Stomatitis			
subjects affected / exposed	7 / 44 (15.91%)	4 / 61 (6.56%)	
occurrences (all)	7	6	
Vomiting			
subjects affected / exposed	7 / 44 (15.91%)	7 / 61 (11.48%)	
occurrences (all)	10	8	
Constipation			
subjects affected / exposed	9 / 44 (20.45%)	7 / 61 (11.48%)	
occurrences (all)	11	7	
Abdominal pain upper			
subjects affected / exposed	4 / 44 (9.09%)	3 / 61 (4.92%)	
occurrences (all)	4	4	
Abdominal pain			
subjects affected / exposed	7 / 44 (15.91%)	9 / 61 (14.75%)	
occurrences (all)	10	11	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	4 / 44 (9.09%)	2 / 61 (3.28%)	
occurrences (all)	5	3	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	0 / 44 (0.00%)	4 / 61 (6.56%)	
occurrences (all)	0	4	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 44 (4.55%)	5 / 61 (8.20%)	
occurrences (all)	2	6	
Haematuria			
subjects affected / exposed	3 / 44 (6.82%)	1 / 61 (1.64%)	
occurrences (all)	3	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 44 (6.82%)	2 / 61 (3.28%)	
occurrences (all)	4	2	
Back pain			
subjects affected / exposed	4 / 44 (9.09%)	1 / 61 (1.64%)	
occurrences (all)	4	1	
Pain in extremity			
subjects affected / exposed	3 / 44 (6.82%)	4 / 61 (6.56%)	
occurrences (all)	3	5	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 44 (0.00%)	4 / 61 (6.56%)	
occurrences (all)	0	4	
COVID-19			
subjects affected / exposed	3 / 44 (6.82%)	4 / 61 (6.56%)	
occurrences (all)	4	4	
Pneumonia			
subjects affected / exposed	3 / 44 (6.82%)	4 / 61 (6.56%)	
occurrences (all)	3	4	
Rhinovirus infection			
subjects affected / exposed	0 / 44 (0.00%)	4 / 61 (6.56%)	
occurrences (all)	0	4	
Sepsis			
subjects affected / exposed	3 / 44 (6.82%)	2 / 61 (3.28%)	
occurrences (all)	3	2	

Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	6 / 44 (13.64%)	3 / 61 (4.92%)	
occurrences (all)	12	8	
Hyperkalaemia			
subjects affected / exposed	1 / 44 (2.27%)	5 / 61 (8.20%)	
occurrences (all)	2	5	
Hypertriglyceridaemia			
subjects affected / exposed	4 / 44 (9.09%)	0 / 61 (0.00%)	
occurrences (all)	14	0	
Hyperuricaemia			
subjects affected / exposed	1 / 44 (2.27%)	8 / 61 (13.11%)	
occurrences (all)	1	10	
Hypoalbuminaemia			
subjects affected / exposed	8 / 44 (18.18%)	18 / 61 (29.51%)	
occurrences (all)	10	36	
Hypocalcaemia			
subjects affected / exposed	5 / 44 (11.36%)	11 / 61 (18.03%)	
occurrences (all)	8	26	
Hypoglycaemia			
subjects affected / exposed	3 / 44 (6.82%)	3 / 61 (4.92%)	
occurrences (all)	7	3	
Hypokalaemia			
subjects affected / exposed	17 / 44 (38.64%)	15 / 61 (24.59%)	
occurrences (all)	27	35	
Hypomagnesaemia			
subjects affected / exposed	5 / 44 (11.36%)	5 / 61 (8.20%)	
occurrences (all)	6	6	
Hyponatraemia			
subjects affected / exposed	4 / 44 (9.09%)	6 / 61 (9.84%)	
occurrences (all)	5	7	
Hypophosphataemia			
subjects affected / exposed	5 / 44 (11.36%)	5 / 61 (8.20%)	
occurrences (all)	5	17	
Tumour lysis syndrome			

subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2	5 / 61 (8.20%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2014	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 • Pharmacodynamic sample collection added on Day 29 of Induction.
23 January 2015	• 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 pharmacodynamics 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.
20 October 2016	• Clarify the target number of participants 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 o Add text clarifying that the carfilzomib dose modification guidelines also apply to the Optional Consolidation Cycle o Add dose modification guidelines for daunorubicin • Add Section 8.6 (Product Complaints) • Revise Section 9 (Supportive Care Requirements and Guidelines) to o Clarify that fungal prophylaxis must be provided during periods of neutropenia o Correct definition for fever and neutropenia o Update Section 9.14 (Contraception) • Update Section 12.6 (Pregnancy and Lactation Reporting) • Add guidelines for taking temperature and blood pressure of participants • Add Section 15.7 (Publication Policy) • Update Section 3 (Background Information) • Make minor text clarifications, additions, and edits throughout the protocol.

20 October 2016	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 participants at the defined MTD. • Revise eligibility criteria to o Include enrollment of participants 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 o Include the enrollment of participants with any first relapse of T-ALL, removing the limitation to those with an early relapse o Modify definition of adequate liver function o Specify grade of pancreatitis as an exclusion criterion o Clarify evidence for bacteria or fungal infection o Clarify antineoplastic agents that are included in prior therapy restrictions.
22 February 2017	The protocol is amended to: • Revise inclusion criteria regarding hepatic function Rationale: Provide clarity that participants 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 participants 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, participants will receive 20 mg/m2 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.

11 September 2017	The protocol is amended to: • Modify the language for dexamethasone dose instruction in the VXLD regimen from 6 mg/m2 twice daily to 6 mg/m2 per day BID – given orally (3 mg/m2 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 participant 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.
24 October 2018	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.

19 September 2019	The protocol is amended to: • To add hepatitis B testing at screening for all participants and at the safety follow up for participants with positive hepatitis B serology at screening or past history of HBV infection. Participants 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 participants with first refractory bone marrow relapse occurring any time after original diagnosis after achieving a CR (ie, ≥ 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 participants should be in a rested and calm 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.
13 August 2020	The protocol was amended as follow: • Addition of the phase 2 part to the existing phase 1 study to allow currently participating sites to seamlessly continue to enroll participants without a break in availability of this therapy for participants 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.

04 February 2021	• 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 participant 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 ≥ 30% > not 30%. • A correction was made to the inclusion criterion that life expectancy must be 6 weeks not ≥ 6 weeks. • Clarification was added to the exclusion criterion that participants 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 participants 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.
04 February 2021	• 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 participants 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 participants and those who are CMV positive, and to further clarify that CMV testing is recommended for all participants. • Clarification was added to the schedule of assessments that participants 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.

04 February 2021	• Clarification was added that chest imaging is only required for participants with a mass present at screening. • Pharmacodynamic blood sample collection was added at 60 minutes after the end of carfilzomib infusion on day 1 of induction to better monitor proteasome inhibition. • Pharmacodynamic and 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 participants 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.
04 February 2021	• 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 participants 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.

04 February 2021	The protocol was amended as follow: • The recommended phase 2 dose of 20/56 mg/m2 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 participants ≥ 12 months, the dose of daunorubicin during induction was changed from 25 mg/m2 for 4 doses to 60 mg/m2 and the dosing frequency was decreased from 4 times to once per cycle (reduced total dose from 100 to 60 mg/m2). 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 participants 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.
03 August 2021	The protocol was amended as follow: • Remove the pharmacogenetic biomarkers from the exploratory objectives in phase 2. • Update inclusion criterion #114 to allow participants 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 participants 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 participants 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 participants 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 participants less than 12 months of age at screening receiving Berlin-Frankfurt-Munster consolidation therapy. • Administrative, typographical, and formatting changes were made throughout the protocol.

04 November 2022	The protocol was amended as follow: • 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 participant but expose the participant to potential risk. This flexibility is expected to reduce post-enrollment eligibility deviations and facilitate enrollment. • Update minimum enrollment numbers of participants 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 participants 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. • 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 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, CRp, CRh, and CRi after consolidation therapy.
04 November 2022	• 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 participants 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.

04 November 2022	• 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 participants to align with exclusion criteria) • Update investigator list on the cover page • Typographical and formatting issues were corrected throughout the document.
28 August 2023	The protocol was amended as follow: • 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) participants and approximately 60 T-cell ALL participants from 90 and 70 participants, 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 participants, 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The information presented is for the Phase 2 part of study 20140106.

Notes: