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Review Completion Date	May 21, 2025
Established Name	Carfilzomib
Trade Name	Kyprolis
Applicant	Onyx Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen Inc.
Formulation(s)	Intravenous, for injection
Dosing Regimen	N/A
Applicant Proposed Indication(s)/Population(s)	N/A
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	N/A

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Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology

OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PWR	Pediatric Written Request
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1 Product Introduction

Proper Name:	Carfilzomib
Trade Name:	Kyprolis
Dosage Forms:	Injection, lyophilized powder in single dose vial for reconstitution at 10mg, 30mg, or 60mg
Therapeutic Class:	Antineoplastic
Pharmacologic Class:	Proteasome inhibitor
Mechanism of Action:	Binds to the N terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome and has antiproliferative and proapoptotic activities *in vitro* in solid and hematologic tumor cells.

Carfilzomib is a proteosome inhibitor approved for patients with relapsed or refractory multiple myeloma as a single agent or in combination therapies. The purpose of the current submission is to provide results of the requested pediatric studies included in a Pediatric Written Request (PWR) that was initially issued on March 17, 2015, with a final amendment issued on August 1, 2012. Carfilzomib was studied in combination with chemotherapy for the treatment of relapsed or refractory (R/R) acute lymphoblastic leukemia (ALL) in children.

1.2 Conclusions on the Substantial Evidence of Effectiveness

Study 20140106 was a Phase 1b/2, open-label, single-arm, multicenter study of patients aged 1 month to 21 years with R/R B-cell and T-cell ALL who received carfilzomib in combination with chemotherapy backbone (CFZ-VXLD) compared to a relevant, contemporary external control. Efficacy of carfilzomib in combination with chemotherapy for R/R ALL was not established in this study. The review team recommends regular approval for this supplemental NDA to update the pediatric use Section 8.4 of the prescribing information to adding a description of the study conducted and that no new safety signals were identified based on the review of the pediatric study.

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Study 20140106 was a Phase 1b/2, open-label, single-arm, multicenter study of patients aged 1 month to 21 years with R/R B-cell and T-cell ALL who received carfilzomib in combination with chemotherapy backbone (CFZ-VXLD) compared to a relevant, contemporary external control. A total of 140 patients were enrolled on Study 20140106. The primary efficacy analysis included 105 patients: 61 with B-cell ALL and 44 with T-cell ALL who received intravenous, twice a week, carfilzomib (20/56 mg/m^2) for three weeks, in combination with induction chemotherapy backbone. After completion of induction cycle, patients had the option of undergoing an additional consolidation cycle if patients had stable disease (SD) or better response at the end of induction cycle. B-cell and T-cell phenotype cohorts were analyzed separately. In the B-cell ALL cohort, the median age (years) was 9 (range 1.2 – 19.0). In the T-cell ALL cohort, the median age (years) was 10.6 (range 3 – 19).

The primary efficacy endpoint of the Phase 2 portion of the study was proportion of patients that achieve complete remission (CR) at the end of induction cycle of therapy compared to weight adjusted CR rate of a relevant, contemporary, external control of pediatric patients who received qualifying salvage regimen for R/R ALL using propensity score analyses. The superiority of carfilzomib (CFZ) in combination with VXLD chemotherapy (CFZ-VXLD) for the treatment of B-cell and T-cell R/R ALL was not established. Of the 61 patients with B-cell ALL in the CFZ-VXLD, 9 (14.8%, 95% CI: 5.9, 23.7) patients achieved CR at the end of induction therapy compared to 4.6 (7.8%, 95% CI: 1.0, 14.7) of the 59.3 patients in the weighted external control arm at the end of the qualifying therapy with an odds ratio (CFZ-VXLD vs. weighted external control, 95% CI) of 2.039 (0.543, 7.658). Of the 44 patients with T-cell ALL in the CFZ-VXLD arm, 6 (13.6%, 95% CI: 3.5, 23.8) achieved CR at the end of induction therapy compared to 4.1 (9.1%, 95% CI: 0.7, 17.5) of the 44.6 in the weighted external control arm at the end of the qualifying therapy, with an odds ratio (CFZ-VZLD vs. weighted external control, 95% CI) of 1.580 (0.470, 5.308). Despite the trend toward higher CR rates in the CFZ-VXLD arm compared to the external control, the confidence interval crossing the threshold of 1 lack statistical significance needed to support efficacy of carfilzomib in combination with chemotherapy for R/R ALL population in this study. Thus, the study did not meet its primary endpoint.

Key secondary endpoints of the Phase 2 portion of Study 20140106 were duration of remission (DOR), event-free survival (EFS) and overall survival (OS). EFS was measured from initiation of therapy until treatment failure, relapse, or death to any cause, whichever occurred first. Comparison of time to event endpoints to historical control data is challenging. However, EFS and OS had a worse trend in the CFZ-VXLD arm versus the weighted external control arm for both the B-cell ALL and T-cell ALL cohorts. The study was not designed in a manner that allows isolation of the treatment effect of carfilzomib and failed to demonstrate sufficient efficacy in either disease cohort. Thus, the study would not be adequate to support an indication for treatment of pediatric patients with R/R B-ALL or T-ALL. With respect to safety, the safety profile was consistent with that of the chemotherapy backbone and the known adverse reactions with carfilzomib already described in the USPI. No new or

more severe adverse events were observed. Section 8.4 of the USPI should note that the safety and effectiveness of carfilzomib in combination with chemotherapy was assessed but not established in pediatric patients in Study 20140106.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ALL accounts for 30% of all childhood cancers with about 3,000 cases/year in the US • 10-20% of patients relapse or remain refractory with a 5-year overall survival <50% for first relapse and <30% for second or greater relapse	R/R ALL is a serious and life-threatening disease.
Current Treatment Options	• Immunotherapies, such as blinatumomab and CAR-T, have improved outcomes in the relapsed setting for B-cell ALL, however, post-immunotherapy relapses remain difficult to treat. • Relapsed T-cell ALL have limited effective treatment options, generally consisting of multiagent chemotherapy or clinical trials.	There is a need for effective agents for the treatment of R/R ALL.
Benefit	• In Study 20140106, 105 patients with R/R B-cell and T-cell ALL were treated with up to 2 cycles of carfilzomib in combination with chemotherapy backbone and did not meet the primary endpoint in either cohort. • For the 61 patients with B-cell ALL, 14.8% (95% CI: 5.9, 23.7) patients achieved CR versus 7.8% (95% CI: 1.0, 14.7) in the weighted external control arm; odds ratio of 2.039 (0.543, 7.658). • For the 44 patients with T-cell ALL, 13.6% (95% CI: 3.5, 23.8) achieved CR versus 9.1% (95% CI: 0.7, 17.5) in the weighted external control arm; odds ratio 1.580 (0.470, 5.308).	Efficacy of carfilzomib in combination with chemotherapy for treatment of R/R B-cell or T-cell ALL was not established.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety population included 115 patients with R/R B-cell ALL and T-cell ALL treated with carfilzomib (20/56 mg/m^2) in combination with chemotherapy. • Of the 67 patients with B-cell ALL, 23.9% had fatal adverse events. Of the 48 patients with T-cell ALL, 8.3% had fatal adverse events. • The overall safety profile of carfilzomib in combination with chemotherapy was similar to that seen in patients with R/R ALL treated with intensive chemotherapy	No new safety signals or increased incidence of known safety concerns were identified during the review of the study

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable [e.g., Section 6.1 Study endpoints]
☐	Clinical outcome assessment (COA) data, such as	
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	

	□	Observational survey studies designed to capture patient experience data	
	□	Natural history studies	
	□	Patient preference studies (e.g., submitted studies or scientific publications)	
	□	Other: (Please specify):	
□	**Patient experience data that were not submitted in the application, but were considered in this review:**		
	□	Input informed from participation in meetings with patient stakeholders	
	□	Patient-focused drug development or other stakeholder meeting summary reports	
	□	Observational survey studies designed to capture patient experience data	
	□	Other: (Please specify):	
X	**Patient experience data was not submitted as part of this application.**		

2 Therapeutic Context

2.1 Analysis of Condition

Acute lymphoblastic leukemia (ALL) is a serious, rapidly developing, and heterogenous group of lymphoid malignancies that is universally fatal if not treated. ALL arises from malignant transformation of B-cell or T-cell progenitor cells in the bone marrow and thymus. Early B-cell precursor lineage account for 80% of ALL cases while T-cell accounts for 10-15%. With recent advances in multi-agent, risk-directed therapy used to treat newly diagnosed ALL, the 5-year event-free survival (EFS) is 85-90%.[1,2,3] However, about 10-20% of patients remain refractory or relapse, which portends a poor prognosis.[4,5] The 5-year overall survival (OS) after first relapse is between 50-60% and worsens with each subsequent relapses with OS decreasing to 20% for multiply relapsed patients. Development of relapse is thought to be related to clonal evolution where leukemia cells acquire new mutations that drive therapy resistance. Thus, novel therapies that decrease relapses and help improve therapy resistance are vital to improving outcomes.

Relapse is highly dependent on patient-specific risk factors such as age, white blood cell (WBC) count at presentation, and disease-related risk factors such as molecular subtypes and immunophenotype.[4,6,7] Using the Berlin Frankfurt Münster (BFM) group definition, risk factors for poor outcomes after relapse include short duration of first remission, bone marrow involvement at relapse, relapsed T-cell immunophenotype, and minimal residual disease (MRD) positive response following reinduction. For B-cell ALL, the 5-year OS after first relapse is approximately 50% with time-to-relapse, relapse site, age at relapse, and end of induction MRD at initial diagnoses associated with OS.[4,8] For T-cell ALL, the OS is 23-35%, much worse than B-cell ALL, with time-to-relapse, relapse site, and age at initial diagnosis associated with OS.[4,9]

2.2 Analysis of Current Treatment Options

There is no standard of care for treatment of R/R ALL. In general, patients with early relapse or high-risk disease receive reinduction therapy (including chemotherapy and immunotherapy) followed by allogeneic HSCT. Currently approved therapies for R/R B-cell ALL include blinatumomab (CD19-directed), inotuzumab (CD22-directed), and tisagenlecleucel (CD19 CAR T-cells). For R/R T-cell ALL there are limited available approved therapies including nelarabine in combination with chemotherapy. While enrolling on a clinical trial is the preferred approach to treatment of relapsed or refractory disease, there are recommended salvage regimens that can be utilized. For R/R B-cell ALL, recommended regimen includes, UKALL R3, COG AALL01P2, ALL-REZ BFM 90, COG AALL1331 (containing blinatumomab), and clofarabine-containing regimens (clofarabine, cyclophosphamide, and etoposide). For T-cell ALL, recommended regimens include nelarabine-containing, bortezomib-containing, and daratumumab-containing

chemotherapy combinations. Currently, vincristine, corticosteroids, and asparaginases are considered key components of reinduction therapy with the addition of anthracyclines, especially for high-risk patients. The choice of anthracyclines has changed over time from use of mitoxantrone (as was used in COG AALL01P2 regimen) to doxorubicin (VXLD) due to increased risk of potential long-term cardiac toxicities associated with mitoxantrone.

Table 1: Summary of Treatment Armamentarium for Relapsed or Refractory Pediatric Acute Lymphoblastic Leukemia

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA approved					
Blinatumomab	R/R B-cell Ph-negative ALL for patients ≥1 month or older	2014	<45kg: 15 mcg/m^2/day (max 28 mcg/day) ≥45kg: 28 mcg/day	TOWER: 91/271 (34%) CR rate at the end of cycle 1	Cytokine release syndrome, neurotoxicity
Inotuzumab	R/R CD22- positive B-cell ALL ≥1 year and older	2017	Cycle 1: 1.8 mg/m^2/cycle Cycle 2: 1.5 mg/m^2/cycle	INO-VATE ALL: 35/39 (89.7%) MRD negative CR rate	Hepatotoxicity
Tisagenlecleucel	R/R B-cell ALL up to 25 years	2017	≤50kg: 0.2 – 0.5 x 10^6 CAR-positive viable T cells >50kg: 0.1 – 2.5 x 10^6 CAR-positive viable T cells	ELIANA: 40/63 (63%) CR rate	Cytokine release syndrome, neurotoxicity, secondary T-cell malignancies
Nelarabine	R/R pediatric T-ALL or T-LL after 2 or more lines of therapy ≥1 year and older	2005	650 mg/m^2 x 5 consecutive days	5/39 (13%) CR rate	Neurotoxicity
Other regimen					
Nelarabine, etoposide, cyclophosphamide[10]	First relapse or primary refractory T-cell ALL or T-LL	N/A	Nelarabine 650 mg/m^2 and etoposide 100 mg/m^2 and cyclophosphamide 400 mg/m^2 x 5 days	CR rate: 4/12 (33%)	N/A
Clofarabine, etoposide, cyclophosphamide[11]	R/R pediatric ALL	N/A	Clofarabine 40 mg/m^2, cyclophosphamide 400 mg/m^2, etoposide 150 mg/m^2 x 5 days	CR rate: 13/25 (52%) (32% T-cell ALL)	N/A
Vincristine, prednisone, PEG-asparaginase, doxorubicin (VPLD)[12]	First relapse ALL Relapse <36 months Relapse ≥36 months	N/A	Vincristine 1.5 mg/m^2 weekly x4, Prednisone 40 mg/m^2/d day 1-29, PEG-asparaginase 2500 U/m^2 day 2,9,16 and 23, Doxorubicin 60 mg/m^2 x1 dose	- Overall CR rate: 81.2% (first relapse) (N=117) - CR rate: 68% for relapse <36 months (N=63) - CR rate: 96% for relapse ≥36 months (N= 54)	N/A

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The intravenous (IV) formulation of carfilzomib is approved for treatment of multiple myeloma. It was initially approved in July 2012 as monotherapy for patients with multiple myeloma who have received at least two prior therapies, including treatment with bortezomib and an immunomodulator. As per USPI version 2022, carfilzomib is indicated:

- For the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy in combination with
    - Lenalidomide and dexamethasone; or
    - Dexamethasone; or
    - Daratumumab and dexamethasone; or
    - Daratumumab and hyaluronidase-fihj and dexamethasone; or
    - Isatuximab and dexamethasone
- As a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy

3.2 Summary of Presubmission/Submission Regulatory Activity

Carfilzomib has Orphan Drug Designation for treatment of patients with multiple myeloma (granted 1/18/2008) and was therefore exempt from the requirement for pediatric studies under the Pediatric Research Equity Act (PREA) for prior approvals. The submission of the original application for carfilzomib occurred prior to enactment of the Research to Accelerate Cures and Equity (RACE) Act. The Applicant submitted a PPSR in November 2014. FDA issued the original Pediatric Written Request (PWR) on March 17, 2015, to obtain information on the dosing, safety, and efficacy of carfilzomib in children with relapsed/refractory acute lymphoblastic leukemia (ALL). Two studies were included in the final amended PWR:

- Study 1: 20140106 – A phase 1b/2 study of carfilzomib in combination with induction chemotherapy in children with relapsed or refractory ALL. [NCT02303821]
- Study 2: 20180065 – A multicenter, retrospective cohort study of pediatric patients with relapsed or refractory B- and T-cell ALL treated with contemporary salvage therapy.

Study 1 was conducted under IND 147187. The PWR subsequently underwent four additional amendments between 2015 – 2023 after multiple guidance meetings.

3.3 Foreign Regulatory Actions and Marketing History

Carfilzomib has orphan designation with EMA for treatment of patients with multiple myeloma (granted 6/3/2008). The applicant had also been issued a PIP from European Medicines Agency initially on January 27, 2021, to study carfilzomib in combination with induction chemotherapy

in pediatric R/R ALL. The same two studies that were in the PWR with FDA were included in the EMA PIP.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

No new significant issues from other disciplines are pertinent to the clinical conclusions on efficacy and safety and are adequately managed through the agreed upon product labeling.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

No new information is provided in the current application for nonclinical pharmacology/toxicology.

6 Clinical Pharmacology

6.1 Executive Summary

Carfilzomib is approved for the treatment of R/R multiple myeloma in adult patients as a single agent or in combination with other anti-myeloma agents. The approved dosages include: 20/70 mg/m^2 (weekly), 20/56 mg/m^2 (twice weekly), 20/27 mg/m^2 (twice weekly). Detailed dosing information is available in NDA 202714 KYPROLIS U.S. Prescribing Information (USPI). Carfilzomib has not been approved for use in any pediatric indications.

In the current submission, the Applicant seeks to update Section 8.4 Pediatric Use of the USPI to include the results of a pediatric clinical Study 20140106. Of note, the Applicant is not requesting a new indication in the current submission.

The clinical pharmacology review focuses primarily on the pharmacokinetics of carfilzomib in combination with chemotherapy in pediatric patients with relapsed/refractory (R/R) B-ALL compared to adult patients.

The following labeling language are included in Section 8.4 Pediatric Use of the proposed USPI:

"The safety and effectiveness of Kyprolis in pediatric patients have not been established. The safety and effectiveness of Kyprolis in combination with chemotherapy was evaluated, but not established in an open label trial (Study 20140106; NCT02303821) in 124 patients aged 1 to younger than 17 years with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) who have received prior targeted B-cell immune therapy or relapsed or refractory T-cell ALL.

No new safety signals were observed in these pediatric patients. The systemic exposure of carfilzomib in these pediatric patients was within range of that observed in adults given the same dose based on body surface area."

6.2 Clinical Pharmacology Assessment

6.2.1 General Pharmacology and Clinical Pharmacokinetics

Briefly, carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib has a half-life of ≤ 1 hour on Day 1 of Cycle 1 following intravenous doses ≥ 15 mg/m^2. The half-life was similar when administered either as a 30-minute infusion or a 2- to 10-minute infusion. Carfilzomib is rapidly metabolized. Peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. Cytochrome P450 (CYP)-mediated mechanisms contribute a minor role in overall carfilzomib metabolism.

Specifically, the selected dose and dosing frequency (i.e., RP2D) of carfilzomib in combination with chemotherapy in Phase 2 portion of Study 20140106 in pediatric patients with R/R ALL is twice weekly as an intravenous (IV) infusion over approximately 30 minutes at a dose of 20 mg/m^2 on day 1 followed by 56 mg/m^2 on days 2, 8, 9, 15, and 16 during induction and at 56 mg/m^2 on days 1, 2, 8, 9, 15, and 16 during the optional consolidation, which is similar to one of the approved dosages in adult patients with R/R multiple myeloma.

6.2.2 Clinical Pharmacology Review Questions

How does the exposure of carfilzomib in pediatric patients compare to that of adult patients at the approved dosages in ALL?

Study 20140106 is phase 1b/2, nonrandomized, multicenter, open-label study evaluating the safety, tolerability, PK, PD, and efficacy of carfilzomib (CFZ) in combination with chemotherapy in children with R/R ALL.

The phase 1b portion of Study 20140106 was a multicenter, nonrandomized, dose-escalation, dose expansion trial of CFZ in combination with induction chemotherapy, comprising of either a dexamethasone, mitoxantrone, PEG-asparaginase, and vincristine (R3) backbone or a VXLD backbone of vincristine, dexamethasone, pegylated asparaginase, and daunorubicin, for the treatment of pediatric subjects with R/R ALL.

The phase 2 portion was a multicenter, single-arm, externally controlled portion of the study designed to evaluate the addition of CFZ to VXLD for the treatment of pediatric subjects with R/R ALL (B- or T-cell) after conventional chemotherapy or targeted immune therapy. Based on review of the totality of data, carfilzomib 20/56 mg/m^2 in combination with VXLD was selected as the RP2D due to toxicity concerns in combination with R3 induction regimen. Details of the study design are listed in 8.1.2.1.

A comparison of post-hoc PK parameter estimates (**Table 2**) from a Population PK model (Appendix 14.1.1) showed that, the geometric least square mean (GLSM) ratio (95%) of population PK model-estimated of carfilzomib PK parameters in pediatric patients (1 to < 17 years) compared to adult patients (21 – 89 years) for BSA effect normalized plasma clearance and volume of distribution were 0.68 (0.58, 0.79) and 0.66 (0.58, 0.75), respectively. The median terminal elimination half-life of carfilzomib in pediatric patients was comparable to that of adult patients (0.99 hour vs. 0.94 hour). The GLSM ratio (95%) of population PK model-predicted C1D8 PK metrics of carfilzomib (**Table 3**) in pediatric patients compared to adult patients for C_{max} and AUC were 115% (95% - 139%) and 120% (99% - 146%), respectively. The PK exposure carfilzomib in these pediatric patients (**Figure 1**) was within range of that observed in adults given the same dose based on body surface area.

Table 2: Carfilzomib PK parameter estimates between adult and pediatric patients

PK Parameter	**Adult** Median (90 percentile)	**Pediatric*** **(ages 1 to < 17)** Median (90 percentile)	**Ratio of pediatric* to adults** (GLSM ratio^ and 95% CI)
N	1788	118	
BSA	1.9 (1.2 - 2.82)	1 (0.4 - 1.9)	0.52 (0.49-0.55)
Plasma clearance, CL (L/hr)	210 (79 - 817)	120 (25 - 347)	0.48 (0.41-0.57)
BSA effect normalized Plasma clearance CL/(BSA/1.88)^a, (L/hr)	207 (79 - 803)	166 (31 - 425)	0.68 (0.58-0.79)
Volume of plasma compartment, V1 (L)	19 (10 - 84)	14 (5 - 47)	0.66 (0.58-0.75)
Half life, $t_{1/2}$ (hr)	0.99 (0.76 - 1.46)	0.94 (0.74 - 1.7)	0.99 (0.95-1.04)
BSA exponent, a = 0.516			

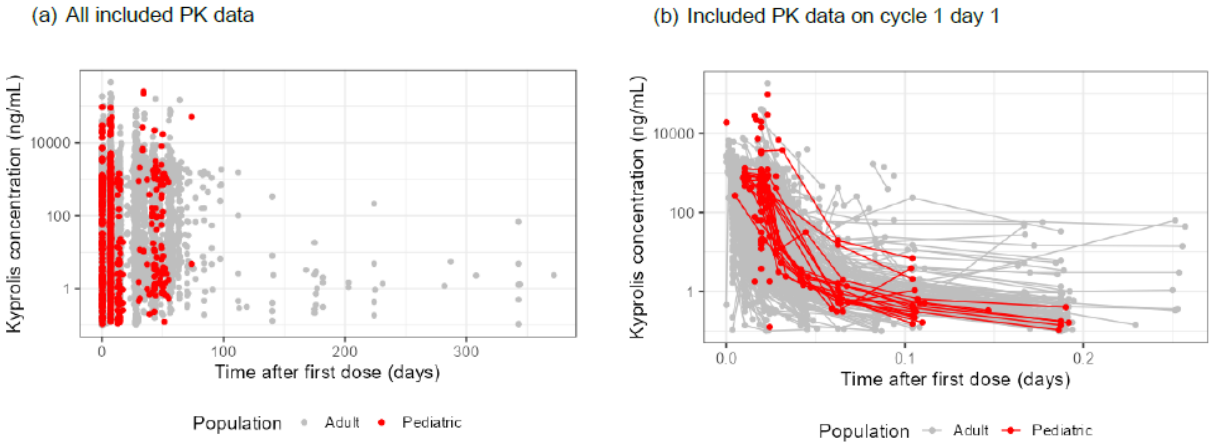
Source: Updated Pharmacometrics Report: 159864 (SDN 1945) Section 10 Table 6c.

Table 3: Comparison of Model predicted carfilzomib PK metrics on C1D8 between adult and pediatric patients

PK metric	Adult Median (90 percentile)	Pediatric* (ages 1 to < 17) Median (90 percentile)	Ratio of Pediatric* to Adult (GLSM ratio^ and 95% CI)
N	816	83	
BSA	1.88 (1.5 - 2.23)	0.9 (0.5 - 1.7)	0.52 (0.48-0.56)
AUC (C1D8) hr*ng/mL	510 (98 - 1524)	473 (196 - 3340)	1.2 (0.99-1.46)
Cmax (C1D8) ng/mL	959 (164 - 2637)	870 (308 - 4169)	1.15 (0.95-1.39)

Source: Updated Pharmacometrics Report: 159864 (SDN 1945) Section 10 Table 6d.

Figure 1: Concentration time profiles of pediatric patients in Study 20140106 overlaid with historical data from adult studies



Source: Updated Pharmacometrics Report: 159864 (SDN1945) Section 11 Figure 4.

The Applicant also conducted E-R analyses for efficacy and safety. Briefly, a flat relationship was demonstrated between carfilzomib exposure (AUC and C_{max}) and the rate of CR or composite CR at the end of the induction cycle. No differences in exposure-efficacy relationships were observed between pediatric subjects with B-cell versus T-cell ALL. In subjects with B- and T-cell ALL who received carfilzomib in combination with VXLD, there were no associations between carfilzomib exposure and all safety endpoints, except for neutropenia vs $AUC._{C1avg}$ in the B-cell ALL population. Given that the Applicant does not plan to pursue pediatric usage, the E-R analysis results were briefly summarized in Section 14.1.2 Exposure-Response analysis.

7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

Table 4: List of Relevant Clinical Studies

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
20140106 (Study 1, phase 2)	02303821	Phase 2, single arm, open-label, multicenter, externally controlled	Induction (28-days): 20/56 mg/m^2 IV on day 1,2,8,9,15, and 16 Consolidation (28-days): 56 mg/m^2 IV on day 1,2,8,9,15, and 16	Primary: CR rate at the end of induction Secondary: safety and tolerability, EFS, OS, DOR	33 months (9/9/2021 – 6/28/2024)	Total: 106 B-cell: 62, 1 enrolled but not treated T-cell: 44	R/R ALL (B- or T-cell)	106 centers located in Argentina, Australia, Austria, Brazil, Bulgaria, Canada, Chile, Colombia, Czech Republic, Denmark, France, Greece, Hong Kong, Italy, Mexico, Netherlands, Norway, Poland, Portugal, Romania, Russia, Saudi Arabia, Singapore, South Africa, South Korea, Spain, Sweden, Taiwan, Thailand, Turkey, and US
20180065 (Study 2)	N/A	Retrospective cohort (to derive an external control for Phase 2 of 20140106)	N/A	Primary: CR rate at the of induction Secondary: EFS, OS	B-cell ALL: 2008 - 2023 T-cell ALL: 2000 - 2023	Total: 612 B-cell ALL: 486 T-cell ALL: 126 For comparative	R/R ALL (B- or T-cell)	22 centers located in US and Australia

						analyses: B-cell ALL: 80 T-cell ALL: 60		
Studies to Support Safety								
20140106 (Study 1, phase 1b)	02303821	Phase 1b (dose escalation/dose expansion) and phase 2	Dose-escalation: Carfilzomib + R3 backbone; carfilzomib + VXLD backbone Dose expansion /Phase 2: Carfilzomib + VXLD backbone	Safety and tolerability MTD/RP2D	112 months (2/12/2015 – 06/28/2024)	Phase 1b: 36 Phase 2: 105	R/R ALL (B- or T-cell)	25 centers located in Australia, Austria, Canada, Denmark, France, Israel, Italy, Spain, United Kingdom, and US
	Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							

7.2 Review Strategy

Study 20140106 (Study 1) was the primary study evaluated in this supplement. This was a phase 1b/2 study of carfilzomib in combination with chemotherapy for the treatment of pediatric patients with R/R ALL. A second study, Study 20180065 (Study 2), was also submitted, which was a retrospective, cohort study to provide an external control for efficacy analyses for Study 1. The primary analysis set (PAS) derived from Study 2 was used to compare to the patients treated with carfilzomib in combination with chemotherapy Phase 2 of Study 1. The datasets for both studies were not independently analyzed because the supplement is not intended to support a new indication. Thus, the protocol, statistical analysis plan (SAP), clinical study reports (CSR), and summary of clinical efficacy were used to describe the patient population and results of the studies. The Applicant's analyses will be used to present the efficacy data with reviewer's commentary regarding their interpretation.

Data Quality and Integrity: Sponsor's Assurance

The Sponsor assured data quality and integrity by the following:

- All patient data related to the study was collected with CRF unless transmitted to the Sponsor or designee electronically (i.e., Laboratory data or centrally adjudicated data)
- Clinical monitors performed source data verification to confirm that CRF data submitted by authorized personnel was accurate, complete, and verifiable safety and rights of patients are being protected, study being conducted by approved protocol and ICH GCP
- The Sponsor representatives performed audits including site inspections, review of records
- Requirement was made of investigators to maintain source documents used to provide data for CRF
- Confidentiality of records identifying study participants related to study data collection and study publications was ensured

Compliance with Good Clinical Practices
Applicant has provided attestation that the studies were conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP)[1].

Financial Disclosure
Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.

The Sponsor certifies that it has not entered any financial arrangements with the clinical

[1] See Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance

investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined by 21 CFR 54.2(a).

Additionally, the Sponsor certifies that each clinical investigator has adequately disclosed financial interests and arrangements.

8 Review of Relevant Individual Trials Used to Support Efficacy

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Data and Analysis Quality

The data discussed in this review is based primarily on the review of final CSR as reported by the Applicant. Additional documents that were reviewed include the protocol and its amendments, and the statistical analysis plan (SAP). Datasets were submitted but not independently analyzed because the study design and results are not intended to support a new indication in the adult or pediatric population. Additionally, carfilzomib does not have an approved indication in the adult population for treatment of ALL from which efficacy in the pediatric population can be extrapolated. Because the Applicant is not seeking a new indication, OSI site inspections were not performed for this supplemental application.

8.1.2 Evaluation of Efficacy

8.1.2.1 Study Design and Endpoints

8.1.2.1.1 Study 20140106

8.1.2.1.1.1 Trial Design

Phase 1b:

The phase 1b portion was a non-randomized, open-label, multi-center, dose escalation/expansion study of carfilzomib in combination with chemotherapy backbone for patients ≥1 year to 20 years with R/R ALL. Initial chemotherapy backbone, R3, was changed to VXLD chemotherapy backbone due to increased toxicities noted during dose escalation. Dose escalation design used Bayesian 2 parameter logistic regression model with a cohort size of 3 and posterior probabilities of the estimated DLT rate to fall into target toxicity level (20 – 33%) or excessive/unacceptable toxicity interval (>33 to 100%). After each cohort completed the induction cycle, CSRC reviewed the safety data to determine whether to escalate, deescalate or expand the dose level. An independent DMC reviewed safety of all patients every 6 months and provided recommendations on study conduct and modifications of study regimen.

Phase 2:

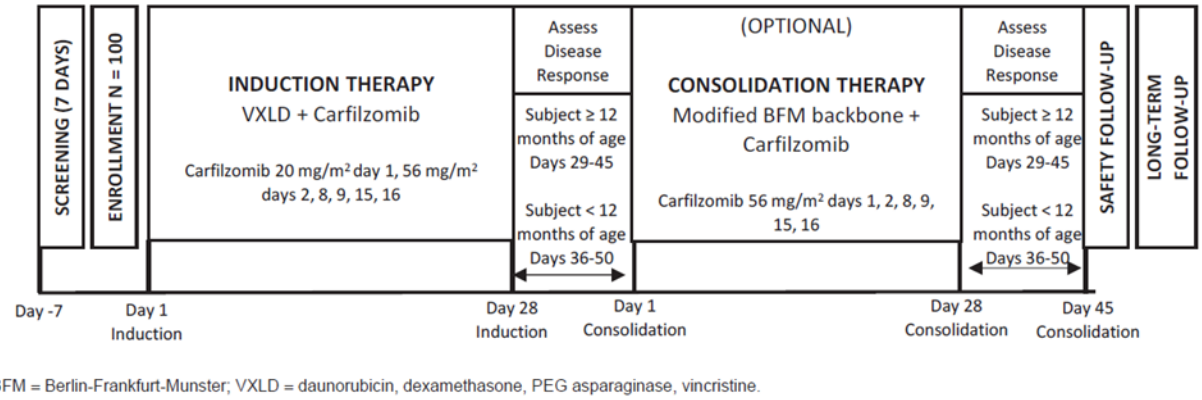


Figure 2: Phase 2 Study Schema
Source: CSR Figure 8-1

Phase 2 of the Study 1 enrolled patients with R/R ALL after meeting eligibility criteria for an induction cycle and an optional consolidation cycle, each lasting 28 days. Induction therapy was carfilzomib 20mg/m^2 (Day 1 of induction only) and 56 mg/m^2 (all other doses), the recommended Phase 2 dose (RP2D), in combination with VXLD chemotherapy backbone. Consolidation therapy was carfilzomib 56 mg/m^2 in combination with modified BFM (cytarabine, 6-mercaptopurine, cyclophosphamide, PEG-asparaginase, vincristine) chemotherapy backbone. Patients underwent disease response evaluation after each cycle.

The study schema in **Figure 2** provides an overview. The phase 2 portion of Study 20140106 (Study 1) was a single-arm, multicenter, non-blinded study to evaluate the addition of carfilzomib (CFZ) in combination with vincristine, dexamethasone, PEG-asparaginase, and daunorubicin (VXLD) chemotherapy backbone (CFZ-VXLD) for the treatment of pediatric patients with R/R B-cell or T-cell ALL.

An interim analysis for non-binding futility assessment for the primary endpoint (CR after induction therapy) was conducted independently for each phenotype (T-cell and B-cell) when 60% of the planned number of subjects from the experimental CFZ-VXLD arm had received at least one dose of CFZ and had the opportunity to complete a post induction response evaluation. All available subjects from the external control arm by this time point were included in this interim analysis. The futility criteria were derived such that the probability of futility is at least 70% under H0 and the power loss (defined as the probability of incorrectly stopping the trial for futility at interim analysis yet succeed at the final analysis) is at most 0.01 under H1, using a Bayesian predictive probability approach.

8.1.2.1.1.2 Study Population

The study population consisted of pediatric patients with R/R B-cell and T-cell ALL as defined as ≥5% leukemia blasts in the bone marrow, with or without extramedullary disease after having achieved at least one prior remission defined as ≤5% leukemia blasts in bone marrow.

Phase 1b:

Key eligibility criteria for Phase 1b were patients age ≥1 year to ≤20 years at the time of treatment initiation, early relapse of B-cell ALL or any T-cell ALL relapse or refractory disease after at least one induction attempt. Phase 1b was conducted in Australia, Austria, Canada, Denmark, France, Israel, Italy, Spain, United Kingdom, and US.

Phase 2:

For the Phase 2 portion of the study, a minimum of 100 participants were planned to be enrolled with a minimum of 30 participants with R/R T-cell ALL and 50 participants with post-immunotherapy R/R B-cell ALL. This was a multi-regional study with centers located in US, Australia, Europe, Asia, and South America.

Key exclusion criteria included patients who had received prior treatment with carfilzomib, allogeneic HSCT within 3 months prior to start of study treatment, active GVHD, less than 30 days from discontinuation of immune suppressive therapy for the treatment of acute or chronic GVHD, isolated extramedullary relapse, active infection, trisomy 21, and another active malignancy. Patients with certain high-risk subtypes of ALL including Philadelphia chromosome positive ALL were not explicitly excluded from enrolling on the study.

8.1.2.1.1.3 Treatment Regimen

Phase 1b:

The initial chemotherapy backbone, R3, consisting of vincristine (1.5 mg/m^2 day 3, 10, 17, 24), polyethylene glycol (PEG) asparaginase (1000 IU/m^2, day 3, 18), mitoxantrone (10 mg/m^2 day 1, 2), and dexamethasone (20 mg/m^2 d 1-5, 15-19), was switched to VXLD backbone. The regimen of carfilzomib with VXLD backbone was same for Phase 1b and 2 as stated below.

Phase 1b/2:

Eligible patients were treated with carfilzomib in combination with VXLD chemotherapy backbone during a 28-day induction followed by bone marrow assessment between days 29 – 45 (days 36 – 50 for infants) based on blood count recovery but prior to start of post-induction therapy. If participants did not have disease progression, they could receive one additional cycle of carfilzomib in combination with consolidation chemotherapy at the investigator's

discretion. The consolidation phase of therapy was followed by another bone marrow assessment between days 29 – 45 (36 – 50 days for infants) based on count recovery.

Carfilzomib in combination with VXLD (vincristine 1.5 mg/m^2, doxorubicin 60 mg/m^2, asparaginase 2500 units/m^2, dexamethasone 4 mg/m^2) induction backbone was administered twice weekly intravenously at a dose of 20 mg/m^2 on day 1 followed by 56 mg/m^2 on days 2, 8, 9, 15, and 16 during induction phase and at a dose of 56 mg/m^2 on days 1, 2, 8, 9, 15, and 16 during the consolidation phase. The consolidation phase chemotherapy consisted of a 28-day modified BFM (mBFM) backbone with cytarabine, 6-mercaptopurine (6-MP), cyclophosphamide, PEG-asparaginase and vincristine. In addition, patients received Intrathecal (IT) methotrexate for central nervous system (CNS) disease prophylaxis or triple IT for active CNS disease. The chemotherapy backbone differed for patients <12 months (infants), who received dose and schedule per COG AALL15P1 regimen.

While patients with Philadelphia chromosome positive ALL were not explicitly excluded from the protocol, these patients could not receive concurrently a tyrosine kinase inhibitor while on the study protocol.

Dose modification or discontinuation

Carfilzomib dose modifications, delays and withholding was allowed on the protocol as per USPI. VXLD regimen modifications were also allowed as per standard of care.

Concomitant Medications

Restricted: Anticancer therapies not part of the study treatment regimen, radiotherapy, non-neoplastic investigational products were strictly excluded.

Allowed: Anti-hyperuricemic medications (allopurinol, rasburicase); intravenous fluids; anti-infectives for pneumocystis, fungal, herpes virus, bacterial prophylaxis, and febrile neutropenia; intravenous immunoglobulins; myeloid growth factors; gastritis prophylaxis; antiemetics; constipation prophylaxis; and contraceptives.

Schedule of assessments
The schedule of assessments was included in the protocol and had adequate monitoring for tumor lysis syndrome, anthracycline induced cardiomyopathy with echocardiogram, cytopenia, and response assessments.

Response assessments definitions:

- Complete remission (CR): M1 bone marrow (<5% blasts) with no peripheral blasts, no extramedullary disease, recovered of blood counts (ANC > 750 mcl and platelets >75,000 mcl). CR and peripheral blood counts should be performed within 1 weeks of each other.

- CR without platelet recovery (CRp): CR as above but with insufficiency platelet count recovery (platelets <75,000 mcl)
- CR with incomplete hematologic recovery (CRi): CR as above with insufficient blood counts (ANC <750 mcl and platelets <75,000 mcl)
- Partial response (PR): complete disappearance of circulating blasts and M2 bone marrow (≥5-<25% blasts), no new extramedullary disease sites and with ANC >750 mcl.
- Stable disease (SD): not satisfying PR or has ANC >750 mcl but not CR, CRp, or PR
- Progressive disease (PD): an increase of at least 25% in the absolute number of circulating leukemic cells or bone marrow blasts, new extramedullary disease, with or without ANC or platelets

8.1.2.1.1.4 Study Endpoints

Phase 1b:

- The primary safety endpoint was safety and tolerability of carfilzomib in combination with induction chemotherapy defined by type, incidence, severity, and outcome of AEs, changes from baseline key laboratory analytes, vital signs, and physical findings.
- Determination of maximal tolerated dose (MTD)
- Key secondary endpoints included:
    - Pharmacokinetics parameters
    - Proportion of patients with CR at the end of induction
    - MRD status using next generation sequencing (NGS) < 10^{-3} and <10^{-4} in subjects who achieve CR.

Phase 2:

- The primary efficacy endpoint was the proportion of patients that achieve bone marrow CR at the end of induction phase of therapy compared to weight adjusted CR rate of a relevant, contemporary, external control of pediatric patients with R/R ALL.
- Key secondary efficacy endpoints included:
    - Event free survival (EFS) as defined as time from initiation of therapy until treatment failure, relapse, or death from any cause
    - Overall survival (OS) as defined as time from initiation of therapy until death from any cause
    - CR, CR without platelet recovery (CRp), CR with partial hematologic recovery (CRh), or CR with incomplete hematologic recovery (CRi) at the end of induction
    - Duration of response (DOR) as defined as time from earliest of CR, CRp, CRh, CRi to relapse or death from any cause
    - Occurrence of a hematopoietic stem cell transplant (HSCT) or CAR-T without an intervening relapse after protocol specified therapy.
    - MRD status using next generation sequencing (NGS) < 10^{-3} and <10^{-4} in subjects who achieve CR.

Response was assessed using local and central laboratory review of bone marrow, peripheral blood and differential, and local assessment for sites of extramedullary disease. MRD was assessed by NGS central laboratory review and local evaluation by flow cytometry and/or PCR or NGS when available.

8.1.2.1.1.5 Protocol Amendments

There were 12 amendments, respectively for phase 1b and phase 2 portions of Study 1. The key changes are highlighted in **Table 5**

Table 5: Protocol Amendments for Study 1

Amendment No. (Date)	Key Changes
1 (May 2014)	• Added PK sample collection after carfilzomib infusion • Pharmacodynamic sample collection added on Day 29 induction
2 (January 2015)	• Added details of MRD specimen collection • Removed ≥ Grade 3 peripheral neuropathy from dose limiting toxicity definition • Added information about PRES and required dose modification of carfilzomib • Updated information regarding required contraception and pregnancy testing
3 (October 2016)	• Added a second dose escalation with VXLD backbone and removed R3 induction backbone • Removed Phase 2 portion of the study • Revised eligibility criteria to include patients 21 years and younger at time of initial diagnosis, changed to any T-ALL first relapse instead of early relapse only, • Clarified target number of participants in each age group • Removed bone marrow biopsy requirement during screening • Edited dose modification guidelines for carfilzomib and daunorubicin • Revised supportive care guidelines
4 (February 2017)	• Updated VXLD road map with correct placement of chemotherapy agent placeholders • Added language to clarify dose escalation dose level lists
5 (September 2017)	• Corrected dexamethasone dose from 6 mg/m2 twice daily to 6 mg/m2 per day BID • Changed the language to state no carfilzomib "rechallenge" required for PRES
6 (October 2018)	• Modified stopping criteria for Bayesian algorithm • Added additional dose levels for dose escalation

7 (September 2019)	• Added hepatitis B screening • Added patients with first refractory bone marrow relapse • Excluded patients receiving inotuzumab within 36 days of start of therapy • Added NGS testing for MRD assessment at the end of induction • Final analyses database will be cleaned, processed, and locked
8 (August 2020)	• Added Phase 2 portion of the study • Amended primary objective to determine MTD and RP2D of carfilzomib in combination with chemotherapy
9 (February 2021)	• RP2D of carfilzomib identified from Phase 1b was added. • Change in total dose of daunorubicin dose from 100 mg/m2 to 60 mg/m2 for induction. • Rationale for changes to VXLD regimen was added • Objectives, endpoints, and analysis sets of the phase 2 portion were aligned with SAP • Clarified assessment of response is MRD by next generation sequencing (NGS) of bone marrow aspirate/peripheral blood would be centrally reviewed, while local assessments will be done for MRD by flow cytometry and extramedullary disease • Added cytomegalovirus (CMV) polymerase chain reaction (PCR) testing at screening • Minor updates in the statistical plans including missing baseline data handling, subgroup analyses, sensitivity analyses • Minor changes in dose modification guidelines added for carfilzomib and updates in supportive care requirements • Minor changes related to chemotherapy backbone and intrathecal chemotherapy omission, dose reductions, and acceptable replacements per standard of care • Treatment response definitions updated including non-evaluable patients to align with Agency' definition • Minor changes in the inclusion/exclusion criteria • Minor changes in schedule of assessments including analyte measured and timing of bone marrow assessments in infants • Minor changes in PK/PD sampling
10 (August 2021)	• Updated exclusion criteria to allow inclusion of patients who received blinatumomab for MRD positive first CR during consolidation or induction failure to achieve first CR • Added use of asparaginase Erwinia chrysanthemi recombinant (Rylaze) to replace PEG-asparaginase or Erwinia asparaginase for infants • Minor changes to the required assessments, schedule of activities, screening guidelines

11 (November 2022)	• Allow routine care procedures obtained within 7 days before enrollment to satisfy screening requirements to decrease potential harm to patients and rescue post-enrollment eligibility deviations • Updated minimum enrollment numbers of T-cell ALL and B-cell ALL patients for Phase 2 of study and external control arms • Revised description of primary endpoint and secondary endpoints related to CR • Removed exclusion criteria that required 3-month window after previous proteasome inhibitors and 2-month window after VXLD. • Extended window to +3 days to allow make up of missed doses of therapy • Updated response definition in alignment with National Comprehensive Cancer Network guidelines (2022)
12 (August 2023)	• Updated minimum number of patients for B-cell ALL to 74 (from 90) and T-cell ALL to 60 (from 70) for the external control arm • Added interim analysis for futility to be done with external control datasets available at the time of analysis. Previously, the entire external control arm dataset was needed

8.1.2.1.2 Study 20180065

8.1.2.1.2.1 Trial Design

Study 20180065 (Study 2) is a retrospective cohort study in collaboration with the Therapeutic Advances in Childhood Leukemia and Lymphoma (TACL) and included 22 sites in US and Australia. Data were collected for all patients that initiated at least one salvage treatment cycle with a curative intent. The study schema for Study 2 is provided below.

8.1.2.1.2.2 Study Population

The overall study population was patients ≤18 years at the time of original diagnosis with R/R B-cell or T-cell ALL who received at least one salvage treatment between January 2000 to February 2023. Of note, B-cell cohort must have initiated salvage regimen between 2012 and 2023 to include patients treated with currently available immunotherapy while T-cell cohort must have initiated salvage regimen between 2000 and 2023. Patients would be followed from initiation of salvage treatment for R/R disease until February 12, 2023. The most recent salvage treatment cycle was included if patients had received multiple salvage attempt. A minimum of 310 patients with B-cell ALL and 100 with T-cell ALL were to be included from the research database. The primary analysis set (PAS) was derived based on the inclusion and exclusion criteria.

Disease definitions:

Relapsed disease was defined as having achieved remission after one or more lines of therapy followed by presenting with marrow disease M2 (5-25% blasts by morphology and ≥ 5% blasts by flow cytometry, fluorescence in situ hybridization (FISH) testing or other molecular method) or M3 (>25% blasts by morphology). Refractory disease was defined as not having achieved remission following one induction or re-induction attempt and presenting with marrow disease M2 or M3.

The specific criteria that were used to include patients in the external control data, also known as the primary analysis set (PAS), were the following:

Inclusion criteria:

- Age ≥ 1 month and <21 years age at the time of qualifying salvage treatment with curative intent
- Must have failed at least one prior therapy as defined by disease status
- No graft-versus host disease within 100 days at the time of treatment
- For B-cell ALL cohort, prior treatment must contain a qualifying immunotherapy (i.e., blinatumomab, inotuzumab, or CAR-T).

Exclusion criteria:

- Mixed phenotype acute leukemia (MAPL)
- Having received other immunotherapies used for B-cell ALL – alemtuzumab, daratumumab, epratuzumab, gemtuzumab, panitumumab
- Salvage therapy with curative intent containing CAR-T or a proteasome inhibitor (i.e., bortezomib, carfilzomib, ixazomib)

8.1.2.1.2.3 Treatment Regimen

The treatment regimen for the external control arm consisted of varied chemotherapy regimen with or without immunotherapy or targeted agents and was not necessarily VXLD for all the patients.

8.1.2.1.2.4 Study Endpoints

Primary endpoint: proportion of patients achieving CR at the end of the re-induction phase

Secondary endpoint:

- proportion of patients achieving CR, CRp, CRh, CRi
- Event free survival: failure to attain CR prior to new therapy, relapse, death.
- Duration of remission (DOR): time from first occurrence of CR/CRh/CRi/CRp after salvage therapy until relapse

- Overall survival: the time from qualifying salvage therapy until death
- MRD negative remission: proportion of patients that achieved CR and were MRD negative
- Proportion of patients who received allogeneic stem cell transplant

8.1.2.1.2.5 Protocol Amendments

There were four total amendments Study 2. The key changes are highlighted in **Table 6**.

Table 6: Protocol Amendment for Study 2

Amendment No. (Date)	Key Changes
1 (March 2020)	• Specificity of analysis sets • Addition of DOR as an objective
2 (August 2020)	• Details related study period • Additions to primary and secondary endpoints – addition of MRD response, CR rates • Clarifications and additions to sensitivity analyses and groups used for it • Added reporting of death events
3 (November 2020)	• Patients with isolated CNS or EM disease to excluded • Primary analyses set (PAS) will only contain the most recent treatment attempt • Missing data will not be imputed and classified as early death or not evaluable • Only one treatment attempt will be analyzed
4 (July 2020)	• End of data collection changed to 2024 from 2021 (due to COVID 19 related restrictions) • Patient sample time period extended to 2021 from 2020 to gather contemporaneous patient population • Defined qualifying versus non-qualifying immunotherapy for B-cell ALL in PAS

8.1.2.2 Statistical Methodologies

All efficacy endpoints were analyzed separately for each phenotype – B-cell or T-cell ALL.

8.1.2.2.1 Sample size determination

The sample size of Study 20140106 Phase 2 was determined based on practical considerations and limited phase 1 data available. Due to the rarity of the subject population, at least 100 subjects were expected to receive at least one dose of carfilzomib in phase 2 part of the study.

A minimum of 50 subjects with B-cell ALL and a minimum of 30 subjects with T-cell ALL were to be enrolled.

The external control arm was selected from Study 20180065 as similar as possible to subjects enrolled in Study 20140106, as described in protocol/statistical analysis plan (SAP). The external control arm was expected to include approximately 74 B-cell ALL subjects and approximately 60 T-cell ALL subjects.

Based on the characteristics of subjects enrolled into the phase 1b part of Study 20140106, and after appropriate propensity score adjustment, the CR rates in the external control arms were expected to be 25% for B-cell and 15% for T-cell subjects respectively, and approximately 60% for B-cell and 30% for T-cell subjects from CFZ-VXLD arm. Based on these assumptions the planned enrollment would provide least 70% power for testing the primary hypothesis for at least one phenotype (B-cell or/ and T-cell) at 2-sided alpha of 0.05 without multiplicity adjustment, with a non-binding interim futility analysis. Additional scenarios are proposed for varying CR rates, sample sizes and the power in the SAP.

8.1.2.2.2 Analysis set and methods

The primary efficacy analysis was based on Primary Analysis Set (PAS), which included all subjects enrolled in the experimental CFZ-VXLD arm who received at least 1 dose of carfilzomib and all external control patients included in the T-PAS/B-PAS as defined in Study 20180065 protocol/SAP. If external control subjects have multiple qualifying therapies, the last qualifying therapy will be chosen.

The treatment response was derived by sponsor based on the local evaluation of bone marrow, peripheral blood, and extramedullary disease status. The comparative analyses were performed with the IPTW adjustment. Comparison of response rates were done CFZ-VXLD versus external control using logistic regression model with inverse probability treatment weights (IPTW) for the average treatment effect of the treated. These weights were derived for each CFZ-VXLD and control subject based on their propensity score (PS) for receiving CFZ-VXLD. **Table 7** lists the prognostic factors included in the PS model. The odds ratio (OR) between the treatment arm and the external control and its 95% confidence interval (CI) were calculated.

Table 7: Prognostic Factors Included in Propensity Score Model for Primary Analysis

Prognostic Factor	Description	Phenotype	Importance Rank
Number of prior relapses	1, 2, >2	T-cell and B-cell	1
Refractory qualifying relapse	Yes, No	T-cell and B-cell	2
Duration of most immediate prior remission (months)	continuous	T-cell and B-cell	3
History of allogeneic hematopoietic stem cell transplant (HSCT)	Yes, No	T-cell and B-cell	4
Relapse time from prior allogeneic HSCT (months) *	continuous	T-cell and B-cell	4

* When value of history of HSCT is No, time from HSCT in months is treated as 0.

Source: Statistical Analysis Plan, Table C-1

The time to event endpoints including EFS, OS and DOR were summarized by Kaplan-Meier (KM) method. DOR analyses only utilized those that had a response during the study. The expected CR rate for the external control were 25% for B-cell ALL and 15% T-cell ALL while expected CR rate for the treatment arm were 60% for B-cell ALL and 30% for T-cell ALL.

No response data was imputed. The missing dates were imputed for adverse events, concomitant medications, death, and anti-cancer therapy as specified in the SAP.

8.1.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Table 8: Summary of Patient Disposition

	B-cell ALL	**T-cell ALL**
Total number of patients	**N = 61**	**N = 44**
Carfilzomib		
Number of patients that completed, n (%)	37 (60.7)	27 (61.4)
Discontinued with reasons	24 (39.3)	17 (38.6)
Death	3 (4.9)	2 (4.5)
Adverse event	17 (27.9)	12 (27.3)
Subject request	0 (0.0)	2 (4.5)
Disease progression	1 (1.6)	0 (0.0)
Requirement for alternative therapy	1 (1.6)	0 (0.0)
Other	2 (3.3)	1 (2.3)
Discontinued from non-investigational products		

Vincristine		
Number of patients that completed, n (%)	34 (55.7)	26 (59.1)
Discontinued with reasons	27 (44.3)	18 (40.9)
Death	6 (9.8)	2 (4.5)
Adverse event	20 (32.8)	12 (27.3)
Subject request	0 (0.0)	2 (4.5)
Disease progression	0 (0.0)	1 (2.3)
Other	1 (1.6)	1 (2.3)
PEG-asparaginase		
Number of patients that completed, n (%)	33 (54.1)	29 (65.9)
Discontinued with reasons	23 (37.7)	12 (29.5)
Death	3 (4.9)	2 (4.5)
Adverse event	19 (31.1)	7 (15.9)
Subject request	0 (0.0)	1 (2.3)
Disease progression	0 (0.0)	2 (4.5)
Other	1 (1.6)	1 (2.3)
Dexamethasone		
Number of patients that completed, n (%)	46 (75.4)	38 (86.4)
Discontinued with reasons	15 (24.6)	6 (13.6)
Death	5 (8.2)	2 (4.5)
Adverse event	6 (9.8)	2 (4.5)
Subject request	0 (0.0)	2 (4.5)
Disease progression	1 (1.6)	0 (0.0)
Requirement for alternative therapy	1 (1.6)	0 (0.0)
Other	2 (3.3)	0 (0.0)
Daunorubicin (or allowed substitutions)		
Number of patients that completed, n (%)	55 (90.2)	42 (95.5)
Discontinued with reasons	2 (3.3)	0 (0.0)
Death	0 (0.0)	0 (0.0)
Adverse event	2 (3.3)	0 (0.0)
Study disposition		
Number of patients that completed, n (%)	19 (31.1)	31 (29.5)
Prematurely discontinued study	42 (68.9)	31 (70.5)
Withdrawal of consent from study	0 (0)	2 (4.5)
Death	42 (62.7)	29 (65.9)
Lost to follow up	1 (1.5)	0 (0.0)

Source: CSR Table 9-1

Aggregate of patient disposition is summarized in **Table 8**. The presented data is from the primary efficacy analysis (PAS) set of Study 1. A total of 106 patients were enrolled in the Phase 2 portion of the study with 62 patients in B-cell ALL cohort and 44 in T-cell ALL cohort. One patient with B-cell ALL was enrolled but did not receive carfilzomib and so total patients that were treated with carfilzomib is 105. All patients were included in the planned analysis.

The first patient was enrolled in (b) (6) and the last patient completed followed up in (b) (6).

Treatment discontinuation: In B-cell ALL cohort, 24 (39.3 %) of 61 discontinued carfilzomib treatment with the most common cause for treatment discontinuation being adverse event (28%). In the T-cell ALL cohort, 17 (38.6%) of 44 discontinued carfilzomib treatment with the most common cause for treatment discontinuation being adverse event (27.3%). Overall, the rates and reasons of discontinuation from carfilzomib were similar in the B-cell ALL and T-cell ALL cohorts. Compared to the non-investigational products, the discontinuation rates were similar for peg-asparaginase and vincristine. Daunorubicin and dexamethasone were better tolerated compared to the other products.

Study discontinuation: For the B-cell ALL cohort, 42 (68.9%) patients discontinued the study. The most common cause for discontinuation was due to death (62.7%). For the T-cell ALL cohort, 31 (70.5%) patients were discontinued from the study due to death. Overall, there was an expected number of patients that did not complete the study as a result of death across both the B-cell and T-cell ALL cohorts.

Protocol Violations/Deviations

Individual narratives of important protocol deviations were not provided. There were 23 (20.0%) patients out of 105 who had one important protocol deviation with a total of 27 total protocol deviations. There were 16 (26.2%) patients in the B-cell ALL cohort and 7 (15.9%) in the T-cell ALL cohort.

Nine (8.6%) patients that entered the study despite the entry criteria were not satisfied. Of these, 3 did not meet T-cell ALL or B-cell ALL relapse criteria, 2 had arrhythmias, 2 had viral infections, and 2 did not meet hepatic function criteria. These patients were placed at increased safety risk as they could have incurred toxicities from chemotherapy and investigational agents that could have been avoided and would have been taken off the protocol for increased toxicities. There were 6 (5.2%) patients with missing data including 3 with missing safety labs and 3 with missing HBV DNA screening. The patients who had missing safety labs would need to be excluded from the safety analysis for laboratory analyses, but given small number, this should not have impacted overall safety outcomes. Missing HBV DNA screening could have put these patients at increased risk for incurring hepatic toxicities if they had unknown active viremia or previous liver damage due to the disease. There were 6 (5.2%) patients who had GCP deviations but without having further details, it is difficult to assess their impact on the study

outcomes including safety. There were 5 (4.8%) who received incorrect dose or compromised investigational product. Three patients received wrong dose of carfilzomib despite having hepatic dysfunction and one patient received higher dose. All three of these patients could have incurred increased toxicities and would have been taken off the study for not tolerating carfilzomib. One patient received compromised product causing harm to the patient such as infection or ineffective product leading to poor efficacy. Finally, 1 patient was kept on study protocol despite being diagnosed with posterior reversible encephalopathy syndrome (PRES) which is an important known adverse effect of carfilzomib and placed this patient at increased safety risk.

Table of Demographic Characteristics

Table 9: Demographic characteristics of the primary efficacy analysis groups

Demographic Parameters	External Control (N= 140) n (%)		CFZ-VXLD (N= 105) n (%)		Total (N= 245) n (%)
	B-cell ALL (N= 80)	T-cell ALL (N= 60)	B-cell ALL (N= 61)	T-cell ALL (N= 44)	
Se					
Male	48 (60.0)	38 (63.3)	42 (68.9)	39 (88.6)	167 (68.2)
Female	32 (40.0)	22 (36.7)	19 (31.1)	5 (11.4)	78 (31.8)
Age group at study entry					
28 days – 23 months	5 (6.3)	1 (1.7)	4 (6.6)	0 (0.0)	10 (4.1)
2 – 11 years	43 (53.8)	37 (61.7)	40 (65.6)	28 (63.6)	148 (60.4)
12- 17 years	27 (33.8)	20 (33.3)	12 (21.3)	13 (29.5)	72 (29.4)
18-64 years	5 (6.3)	2 (3.3)	4 (6.6)	3 (6.8)	14 (5.7)
Race					
White	34 (42.5)	32 (53.3)	38 (62.3)	33 (75.0)	137 (55.9)
Black or African American	7 (8.8)	10 (16.7)	2 (3.3)	2 (4.5)	21 (8.6)
Asian	5 (5.0)	4 (6.7)	9 (14.8)	6 (13.6)	24 (9.8)
American Indian or Alaska Native	2 (2.5)	1 (1.7)	2 (3.3)	2 (4.5)	7 (2.9)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	1 (0.4)
Another [a]	0 (0.0)	0 (0.0)	9 (14.8)	1 (2.3)	10 (4.1)
Multiple [b]	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.4)
Unknown/Not reported	33 (41.3)	12 (20.0)	0 (0.0)	0 (0.0)	45 (18.4)
Ethnicity					
Hispanic or Latino	27 (33.8)	6 (10.0)	28 (45.9)	11 (25.0)	72 (29.4)
Not Hispanic or Latino	39 (48.8)	35 (58.3)	33 (54.1)	33 (75.0)	140 (57.1)
Unknown/Not reported	14 (17.5)	19 (31.7)	0 (0.0)	0 (0.0)	33 (13.5)
Region (optional)[c]					
Region 1	77 (96.3)	59 (98.3)	12 (19.7)	16 (36.4)	164 (66.9)
Region 2	3 (3.8)	1 (1.7)	49 (80.3)	28 (63.6)	81 (33.1)

[a] Includes Afghan, Indian, Brown, Brazilian indigenous, Hispanic Mestizo, Mestizo breed, Hispanic and mixed.
[b] One subject reported white and black/African American
[c] Region 1 includes Australia, Austria, Italy, Spain, US. Region 2 includes Argentina, Brazil, Bulgaria, Chile, Colombia, Greece, Hong Kong, Republic of Korea, Mexico, Portugal, Romania, Russian Federation, Saudi Arabia, Singapore, South Africa, Taiwan, Province of China, Turkey.
Source: CSR Table 9-2, 9-3

Table 9 shows demographic characteristics of patients included in the primary efficacy analysis in the Phase 2 portion of Study 1 versus the external control.

For both B-cell ALL and T-cell ALL cohorts, race representation is different from and do not adequately represent US population. There are likely several reasons for this including that the treatment arm study was a global study with majority of patients in both cohorts being represented from outside of US while the external control was derived from institutions primarily located in the US and Australia. There are also a lot of missing data for race for the external control which also affect the overall representation of race distribution between the two arms. For T-cell ALL cohort, there are significantly fewer females in the treatment arm compared to the external control. Despite these differences, the interpretability of the outcomes of the study should not have been impacted.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 10: Disease characteristics of the primary efficacy analysis group for B-cell ALL

Diseases characteristics	External Control (N=80) n (%)	CFZ-VXLD (N= 61) n (%)
Duration from initial ALL diagnosis (months)		
Mean (SD)	39.6 (29.1)	41.0 (14.9)
Median	30	22.2
Min, Max	3, 165	6.6, 49.9
Number of prior relapses		
1	25 (31.3)	19 (31.1)
2	27 (33.8)	20 (32.8)
≥ 3	28 (35.0)	22 (36.0)
History of primary induction failure		
Yes	10 (12.5)	8 (13.1)
No	69 (86.3)	48 (78.7)
Unknown/missing	1 (1.3)	5 (8.2)
History of allogeneic HSCT		
Yes	27 (33.8)	32 (52.5)
Time from prior allogeneic HSCT (months)		
<6 months	8 (10.0)	9 (14.8)
≥6 months – 12 months	7 (8.8)	15 (24.6)
>12 months	12 (15.0)	8 (13.1)
Unknown/Missing	53 (66.3)	0 (0.0)
Received targeted B-cell immune therapy		
Blinatumomab	49 (61.3)	47 (77.0)
Inotuzumab	23 (28.8)	9 (14.8)
CAR-T	41 (51.3)	12 (19.7)
Other immunotherapy	7 (8.8)	0 (0.0)
Isolated bone marrow at relapse		

Yes	48 (60.0)	40 (65.6)
No	15 (18.8)	21 (34.4)
Unknown/Missing	17 (21.3)	0 (0.0)
CNS status		
Negative	44 (55.0)	47 (77.0)
Positive	10 (12.5)	11 (18.0
Unknown/missing	26 (32.5)	3 (4.9)
Subtype of ALL		
High risk (t (9;22), KMT2A translocation, hypodiploidy [<44 chromosomes)	9 (11.3)	14 (23.0)
Non-high risk	56 (70.0)	37 (60.7)
Unknown/missing	15 (18.8)	10 (16.4)

Source: Summary of clinical efficacy (SCE) Table 6

For the B-cell ALL cohort, the external control group had 7 patients that received proteasome inhibitors in their prior therapy before the salvage attempt, while having received any prior proteasome inhibitor therapy was listed as an exclusion criterion for the treatment arm of the Study 1. More patients in the treatment arm had high-risk subtype of ALL compared to the external control. Otherwise, disease characteristics were comparable between the external control and treatment arms, although there were more unknown/missing data in the external control arm making interpretability about baseline data difficult.

Table 11: Disease characteristics of the primary efficacy analysis group for T-cell ALL

Disease characteristics	**External Control** (N=60) n (%)	**CFZ-VXLD (56 mg/m^2)** (N= 44) n (%)
Duration from initial ALL diagnosis (months)		
Mean (SD)	20 (16.9)	27.8 (19.2)
Median	16	22.1
Min, Max	(2, 95)	(4.3, 99.1)
Number of prior relapses		
1	42 (70.0)	32 (72.7)
2	14 (23.3)	11 (25.0)
≥3	2 (3.3)	1 (2.3)
History of primary induction failure		
Yes	7 (11.7)	14 (31.8)
No	53 (88.3)	30 (68.2)
History of allogeneic HSCT		
Yes	8 (13.3)	18 (40.9)
Time from prior allogeneic HSCT (months)		
<6 months	3 (5.0)	3 (6.8)
≥6 months – 12 months	1 (1.7)	6 (13.6)

>12 months	3 (5.0)	9 (20.5)
Unknown/Missing	53 (88.3)	0 (0.0)
Isolated bone marrow relapse?		
Yes	31 (51.7)	16 (36.4)
No	24 (40.0)	28 (63.6)
Unknown/missing	5 (8.3)	0 (0.0)
CNS status		
Negative	31 (51.7)	28 (63.6)
Positive	21 (35.0)	12 (27.3)
Unknown/missing	8 (13.3)	4 (9.1)
Early T-cell precursor phenotype		
Yes	6 (10.0)	11 (25.0)
No	-	18 (40.9)
Unknown/Missing	-	15 (34.1)

Source: SCE Table 7

For the T-cell ALL cohort, the external control group had 3 patients that received proteasome inhibitors in their prior therapy, while any prior proteasome inhibitor therapy was listed as an exclusion criterion for Study 2. More patients had induction failure and had undergone allogeneic HSCT in the treatment arm compared to the external control. Despite these differences, the interpretability of the outcomes of the study should not have been impacted.

8.1.2.4 Study Results

Primary Endpoint

The primary efficacy endpoint for the Phase 2 portion of the study was the proportion of patients who achieved CR at the end of induction therapy compared to weight-adjusted CR in the external control arm. The primary endpoint was assessed separately for B-cell ALL and T-cell ALL as prespecified in the statistical analyses plan (SAP).

B-cell ALL: In the treatment arm, there were 26 (42.6%) responders and 35 (57.4%) non-responders in the B-cell ALL cohort. Nine (14.8%) out of 61 patients achieved CR at the end of induction. In the external control, there were 25 (31.3%) responders and 55 (68.8%) non-responders. Six (7.5%) out of 80 patients achieved CR at the end of induction. After IPTW adjustment using propensity score, the CR rates were 14.8% (5.9, 23.7) and 7.8% (1.0, 14.7) in the CFZ-VXLD versus external control arm, respectively. The odds ratio (OR) of CFZ-VXLD vs weighted external control was 2.039 (0.543, 7.658). Despite the CR rates being higher for CFZ-VXLD compared to the external control, the primary endpoint did not demonstrate a statistically significant difference between the CFZ-VXLD and the control arm. Notably, the CR rates in both the treatment arm and the external control arm were less than anticipated. Thus, efficacy of carfilzomib in treating pediatric R/R B-cell ALL was not established.

T-cell ALL: In the treatment arm, there were 12 (27.3%) responders and 32 (72.7%) non-responders in the T-cell ALL cohort. Six (13.6%) out of 44 patients achieved CR at the end of induction. In the external control, there were 15 (25.0%) responders and 45 (75.0 %) non-responders. Seven (11.7%) out of 60 patients achieved CR at the end of induction. After IPTW adjustment using propensity score, the CR rates were 13.6% (3.5, 23.8) and 9.1% (0.7, 17.4) in the CFZ-VXLD versus the external control arm. The OR of CFZ-VXLD vs weighted external control was 1.580 (0.470, 5.308). As noted, despite the CR rates being higher in CFZ-VXLD compared to the external control, the primary endpoint did not demonstrate a statistically significant difference between CFZ-VXLD and the external control arm. Thus, efficacy of carfilzomib in treating pediatric R/R T-cell ALL was not established.

Efficacy Results – Secondary and other relevant endpoints

B-cell ALL: For the B-cell ALL cohort, the rate of CRi or better at the end of induction was 42.6% (30.2, 55.0) for CFZ-VXLD and 26.3% (15.1, 37.5) in the external control with OR (treatment arm vs. external control) 2.082 (0.968, 4.477).

Median (95% CI) EFS was 1.18 (0.95, 2.24) months for CFZ-VXLD and 3.63 (1.55, 5.36) months for the weighted external control arm. The Kaplan-Meier estimate of EFS rate (95% CI) at 6 months, 12 months, and 24 months was 26.2% (16.0, 37.6), 16.4% (8.4, 26.7), and 12.5% (5.6, 22.4), respectively for CFZ-VXLD and 35.4% (23.7, 47.2), 24.8% (14.7, 36.4), and 17.9% (9.2, 28.8), respectively for the weighted external control arm. The EFS stratified hazard ratio from a Cox proportional hazard model for CFZ-VXLD versus the weighted external control was 1.435 (95% CI 0.976, 2.111).

Median (95% CI) OS was 5.23 (2.93, 9.24) months for the CFZ-VXLD arm and 8.59 (5.26, 10.59) months for the weighted external control arm. The Kaplan-Meier estimate of OS (95% CI) at 6 months, 12 months, and 24 months was 42.8% (30.0, 55.0), 33.3% (21.5, 45.6), and 27.4% (15.7, 40.4), respectively, for the CFZ-VXLD arm and 57.2% (43.6, 68.6), 36.3% (24.0, 48.7), and 28.6% (17.3, 41.0), respectively, for the weighted external control arm. The OS stratified hazard ratio from a Cox proportional hazard model for CFZ-VXLD versus weighted external control was 1.245 (95% CI: 0.805, 1.927).

T-cell ALL: For the T-cell ALL cohort, the rate of CRi or better at the end of induction was 27.3% (14.1, 40.4) in CFZ-VXLD and 18.6% (7.1, 30.0) in the external control with OR (treatment arm vs. external control) 1.646 (0.639, 4.245).

Median (95% CI) EFS was 1.20 (0.95, 1.48) months for the CFZ-VXLD arm and 2.93 (0.95, 5.10) months for the weighted external control arm. The Kaplan-Meier estimate of EFS rate (95% CI) at 6 months, 12 months, and 24 months was 24.6% (13.1, 38.1), 13.8% (4.7, 27.9), and 13.8% (4.7, 27.9), respectively, for the CFZ-VXLD arm and 23.4% (10.6, 39.1), 16.6% (6.6, 30.4), and 15.4% (6.0, 29.0), respectively, for the weighted external control arm. The EFS stratified hazard ratio from a Cox proportional hazard model for CFZ-VXLD vs weighted external control was 1.404 (95% CI: 0.869, 2.270).

Median (95% CI) OS was 4.51 (3.49, 9.18) months for the CFZ-VXLD arm and 7.04 (4.70, 10.69) months for the weighted external control arm. The Kaplan-Meier estimate of OS event free rate (95% CI) at 6 months, 12 months, and 24 months was 48.8% (32.9, 63.0), 27.9% (14.3, 43.1), and 22.3% (9.3, 38.8), respectively, for the CFZ-VXLD arm and 54.9% (34.2, 71.6), 24.1% (10.9, 40.1), 21.4%(9.4, 36.7), and 18.9% (7.9, 33.5), respectively, for the weighted external control arm. The OS stratified hazard ratio from a Cox proportional hazard model for CFZ-VXLD vs weighted external control was 1.040 (95% CI: 0.641, 1.688).

Durability of Response

B-cell ALL: For the 26.0 subjects (42.6% in the CFZ-VXLD arm who achieved CRi or better, the median (95% CI) duration of remission was 7.55 (3.42, 22.20) months. For the 15.6 patients (26.3%) in the weighted external control arm who achieved CRi or better, the median (95% CI) duration of remission was 8.72 (5.07, 32.24) months.

After the end of protocol therapy, a total of 12 subjects (19.7% [95% CI: 10.6, 31.8]) with B-cell ALL received stem cell transplant or CAR-T without an intervening relapse: 11 subjects (18.0% [95% CI: 9.4, 30.0]) received stem cell transplant, 3 subjects (4.9% [95% CI: 1.0, 13.7]) received CAR-T (2 subjects received both stem cell transplant and CART).

T-cell ALL: For the 14.0 subjects (31.8%) in the CFZ-VXLD arm who achieved CRi or better, the median (95% CI) duration of remission was 9.01 (2.57, NE) months. For the 8.3 patients (18.6%) in the weighted external control arm who achieved CRi or better, the median (95% CI) duration of remission was 5.82 (1.22, 19.80) months.

After the end of protocol therapy, a total of 12 subjects (27.3% [95% CI: 15.0, 42.8]) with T-cell ALL received stem cell transplant or CAR-T without an intervening relapse: 12 subjects (27.3% [95% CI: 15.0, 42.8]) received stem cell transplant, 1 subject (2.3% [95% CI: 0.1, 12.0]) received CAR-T.

For the B-cell ALL cohort, carfilzomib in combination with chemotherapy failed to show durable complete response. For T-cell ALL cohort, there was a higher duration of response in the CFZ-VXLD arm compared to the external control. However, the number of patients that achieved CRi or better was only 31.8% and there was no demonstrable overall survival benefit as noted previously.

8.1.3 Efficacy in Sub-Populations

The subgroup analyses of CR at the end of induction cycle are presented in **Figure 3** for patients with B-cell ALL and **Figure 4** for patients with T-cell ALL. Due to small sample size and the inherent limitation of using external control arm, interpretation of subgroup analyses was limited. Results across all relevant subgroups were generally consistent with those of the primary analysis.

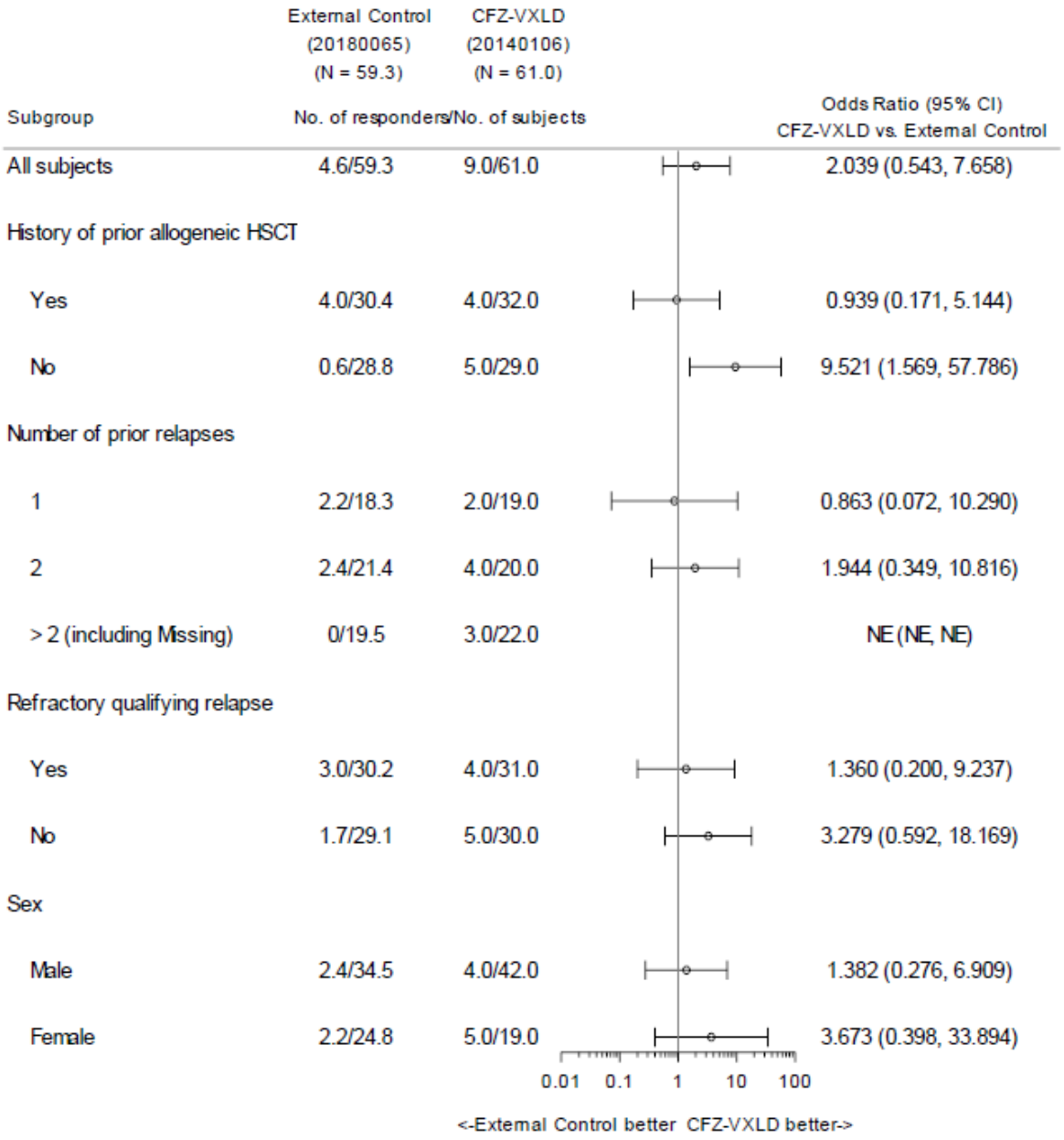


Figure 3: Forest Plot of Subgroup Analyses of CR at the End of Induction (B-cell ALL)
Source: Figure 10-1 in CSR

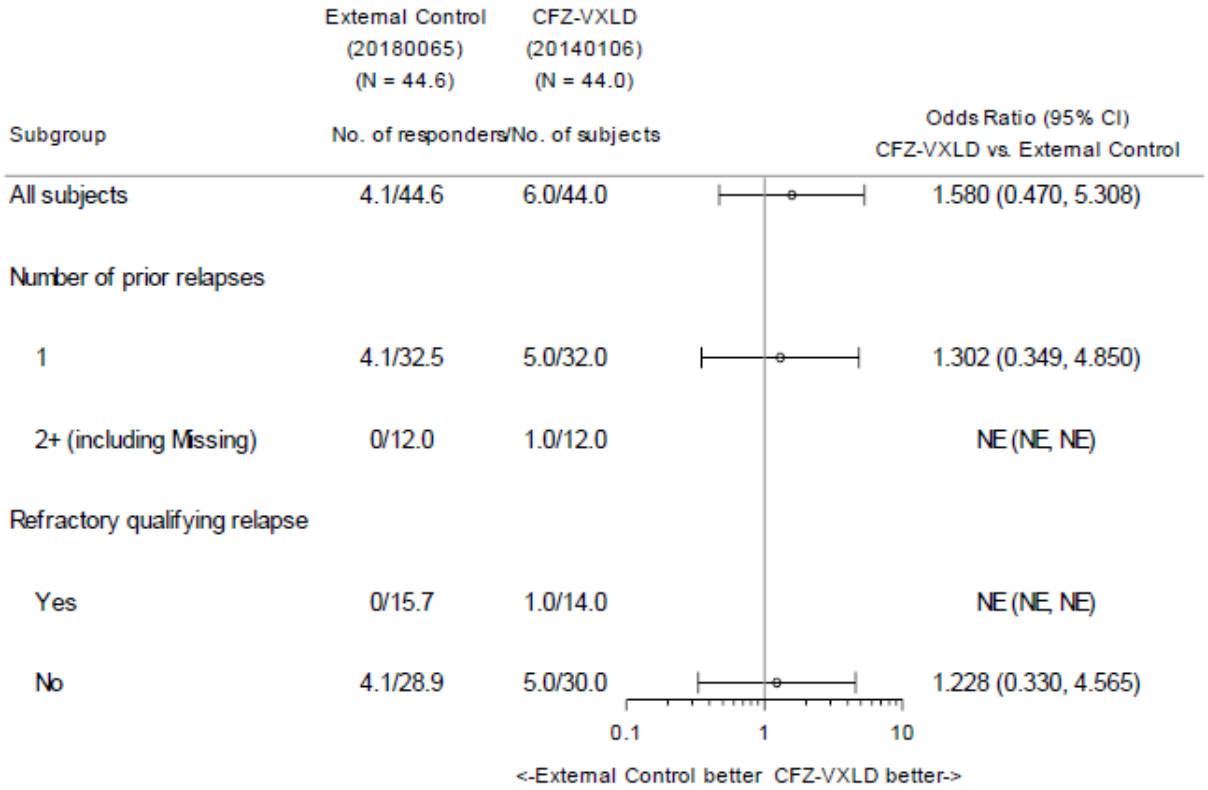


Figure 4: Forest Plot of Subgroup Analyses of CR at the End of Induction (T-cell ALL)
Source: Figure 10-2 in CSR

Above are all the subgroup analysis included in the CSR. Other subgroups pre-specified in the SAP were not submitted, including the following:

- History of prior HSCT (not submitted for T-cell)
- History of primary induction failure
- Relapse time from HSCT
- Early T cell precursor phenotype (for T-cell phenotype only)
- Cytogenetic risk
- Duration of first remission
- Age at diagnosis
- Sex (not submitted for T-cell)
- Isolated BM at relapse
- Blast percent in marrow prior to the qualifying treatment
- Geographical region

8.1.4 Conclusions

The efficacy of carfilzomib in combination with VXLD chemotherapy backbone was studied for R/R B-cell ALL and T-cell ALL in Study 1 and results were compared to a clinically relevant and contemporary external control from Study 2. Study 1 enrolled a total of 106 patients with 62 with R/R B-cell ALL and 44 with R/R T-cell ALL. Study 2 had a total of 140 patients with 80 with

R/R B-cell ALL and 60 with R/R T-cell ALL. The primary endpoint of the proportion of patients that achieve CR assessed at the end induction therapy was analyzed separately for each cohort. The SAP pre-specified expected CR rate for the external control were 25% for B-cell ALL and 15% T-cell ALL while expected CR rate for the treatment arm were 60% for B-cell ALL and 30% for T-cell ALL.

In the B-cell ALL cohort, the IPTW adjusted CR rate (95% CI) at the end of induction in CFZ-VXLD and weighed external control arm was 14.8% (5.8, 23.7) and 7.8% (1.0, 14.7), respectively, with an odds ratio (CFZ-VXLD vs. weighted external control, 95% CI) of 2.039 (0.543, 7.658). In the T-cell ALL cohort, The IPTW adjusted rate of CR (95% Cl) for subjects with T-cell ALL at the end of induction therapy in the CFZ-VXLD and weighted external control arm was 13.6% (3.5, 23.8) and 9.1% (0.7, 17.5), respectively, with an odds ratio (CFZ-XLD vs weighted external control, 95% CI) of 1.580 (0.470, 5.308). The primary endpoint of CR did not meet statistical significance of superiority for carfilzomib in combination with chemotherapy for both cohorts although the proportion of CR rates was higher for CFZ-VXLD group. The presented study was not a concurrently randomized and blinded trial resulting in potential influence of unmeasured biases. In addition, the patient populations had key differences that could have impacted the study outcomes. The CFZ-VXLD group had majority of patients outside of US while the external control was derived from US and Australia which could lead to more heterogeneity of prior therapy received, patient populations, and supportive care standards. In particular, the time-to-event analyses demonstrated that both in the B-cell ALL and T-cell ALL cohorts, the external control arm had higher EFS and OS compared to CFZ-VXLD and could be related to increased carfilzomib discontinuation due to adverse events and increased deaths noted specifically in the B-cell ALL cohort.

The Applicant does not intend to use this study to support an application for a new indication for adults or pediatrics. Additionally, carfilzomib does not have an FDA approved adult indication for ALL or LL from which efficacy for the pediatric population could be extrapolated. Based on this study, it is acceptable to add a description of Study 20140106 to Section 8.4 Pediatric Use of the USPI and may state that the efficacy was evaluated but not established. The data do not support any other changes to the current USPI label other than adding a description of this new study.

8.1.5 Integrated Review of Effectiveness

Efficacy results from the pediatric studies in acute lymphoblastic leukemia were not integrated with any other relevant studies.

8.2 Review of Safety

8.2.1 Safety Review Approach

The safety data of Study 1 were evaluated in this supplement. The datasets were not analyzed because the supplement is not intended to support a new indication. There were no specific

safety review issues that were identified during drug development requiring special evaluation. Furthermore, the safety data of carfilzomib is well-known from its use in adult patients with multiple myeloma. The additional patients on this study provided adequate data to assess for known adverse reactions in the pediatric population. Thus, the protocol, statistical analysis plan (SAP), clinical study reports (CSR), and summary of clinical safety were used to describe the patient population and results of the studies. The Applicant's analyses will be used to present the safety data with reviewer's commentary regarding their interpretation.

Adequacy of the safety database:

Because the Applicant is not seeking a new indication, OSI site inspections were not performed for this supplemental application.

Adequacy of Applicant's Clinical Safety Assessments

Adequate clinical safety assessments were performed during the conduct of the Phase 1b/2 of Study 1:

Screening assessments:

- History and physical examination
- Disease staging with bone marrow aspirate, lumbar puncture and testicular exam
- ECG and ECHO
- Labs: blood counts, liver function, kidney function, pancreatic function; tumor lysis labs, urine pregnancy for females with reproductive potential, and hepatitis B testing

On-study assessments:

- Weekly physical exams
- Weekly labs: blood counts, liver function, kidney function, pancreatic function, tumor lysis labs, glucose measurements

End of study assessments:

- Physical examination
- Labs: blood counts, liver function, kidney function, pancreatic function; tumor lysis labs, glucose measurements, hepatitis B testing

Issues Regarding Data Integrity and Submission Quality

No issues were identified regarding data integrity and submission quality during the conduct of the safety review for this application. Please see Section 8.1.3 for Applicant's reassurances regarding data integrity and submission quality.

Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0. Toxicity grades were derived based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03. AEs and TEAEs were recorded and reported from the time informed consent to the time of follow-up visit, 30 days after the last dose of study treatment. All adverse events were treatment-emergent, defined as events with onset after the administration of the first dose of any study treatment and within the end of study or 30 days of the last dose of any study treatment.

8.2.2 Review of the Safety Database

8.2.2.1 Overall Exposure

Summary of the overall exposure of carfilzomib are described for all patients who received carfilzomib at 20/56 mg/m^2 in combination with VXLD chemotherapy backbone for induction therapy in Phase 2 portion of Study 1. Exposure data from 61 patients with B-cell ALL and 44 patients with T-cell were pooled for these analyses. The median duration of treatment was 16 (2, 23) with average dose per administration of 48.2 mg/m^2 (SD 4.3) and the mean relative dose intensity (RDI) was 96.4 (SD 8.6).

8.2.2.2 Relevant characteristics of the safety population

Phase 1b portion of the study included two separate dose escalation cohorts. Dose escalation 1 (DE1) consisted of patients who received carfilzomib in combination with R3 backbone. However, during the conduct of this study, R3 backbone, which contained mitoxantrone, was deemed overly toxic as 2 out of 4 patients at dose 20/27 mg/m^2 dose of carfilzomib had dose limiting toxicities. CRMC and DSMC for the study 1 made decision to change the backbone to VXLD. Dose escalation 2 (DE2) entailed two DLT-evaluable patients at 20/56 mg/m^2 dose where one patient had pulmonary hemorrhage <24 hours after the first dose of carfilzomib and second patient had Grade 4 thrombocytopenia 2 days after the first dose of carfilzomib. After review of PK/PD data, 20/56 mg/m^2 dose was determined to be the recommended phase 2 dose (RP2D).

The presented safety data were pooled aggregates of patients that received a single dose of carfilzomib at 20/56 mg/m^2 across both phase 1b and phase 2 of Study 1. The safety analyses were performed separately for B-cell ALL and T-cell ALL and pooled when applicable.

Table 12: Safety Population, Size, and Denominators

Safety Database Individuals exposed to the study drug in this development program for the population under review N= 140 (N is the sum of all available numbers from the columns below)			
Cohorts	Phase 1b R3 Backbone (N= 11) (n,%)	Phase 1b VXLD backbone (N= 24) (n,%)	Phase 2 VXLD backbone (N= 105) (n,%)
B-cell	9 (81.8)	13 (54.2)	61 (58.1)
T-cell	2 (18.2)	9 (37.5)	44 (41.9)
Other	0 (0.0)	2 (8.3)	0 (0.0)

Source: Summary of information from CSR Phase 1 and 2

8.2.3 Safety Results

8.2.3.1 Deaths

The investigators did not attribute any fatal events reported to carfilzomib in combination with VXLD. Majority of fatal events were attributed to burden of prior therapy or other disease-related events.

B-cell ALL: Sixteen (23.9%) of 67 patients had fatal adverse events. The reported causes of fatal adverse events by preferred term included septic shock (3%), acute respiratory failure (1.5%), bronchopulmonary aspergillosis (1.5%), COVID-19 pneumonia (1.5%), Escherichia sepsis (1.5%), multiorgan dysfunction syndrome (1.5%), nervous system disorder (1.5%), neutropenic colitis (1.5%), neutropenic sepsis (1.5%), pneumonia fungal (1.5%), pneumonia klebsiella (1.5%), pulmonary hemorrhage (1.5%), pulmonary veno-occlusive disease (1.5%), sepsis syndrome (1.5%) and pneumonia (1.5%).

T-cell ALL: Four (8.3%) out of 48 patients had fatal adverse events. The reported causes of fatal adverse events by preferred term included bronchopulmonary aspergillosis (, Escherichia sepsis, septic shock and multiple organ dysfunction syndrome.

Across both cohorts, the causes of fatal adverse events were expected for relapsed/refractory ALL pediatric patients. However, B-cell ALL cohort had significantly higher incidences of fatal adverse events compared to T-cell ALL cohort. One of the plausible explanations for this could be that the B-cell ALL cohort tended to have multiple prior relapses compared to T-cell ALL cohort leading to increased prior therapy burden, increased sensitivity to toxicities, and increased risk of potential infections due to poor marrow function.

8.2.3.2 Nonfatal SAEs

B-cell ALL: Serious adverse events were reported in 48 (71.6%) of 67 patients with septic shock (9, 13.4%) and febrile neutropenia (9, 13.4%) as the most frequent, followed by pneumonia (5, 7.5%), and sepsis (4, 6.0%).

T-cell ALL: Serious adverse events were reported in 33 (68.8%) of 44 patients with posterior reversible encephalopathy syndrome (PRES) (4, 8,3%) and thrombocytopenia (4, 8.3%) as the most frequent, followed by Escherichia sepsis (3, 6.3%), febrile neutropenia (3, 6.3%), leukopenia (3, 6.3%), pyrexia (3, 6.3%), and septic shock (3, 6.3%).

Across both cohorts, the serious adverse events consisted of mostly infections and complications of infections which is consistent with the adverse events that are noted in clinical practice for patients with R/R ALL receiving intensive chemotherapy. The increased incidence of PRES that was noted in the T-cell ALL cohort is important to highlight as this is a known safety issue of PRES and incidence of this particular AE could have been augmented in patients who are also receiving prolonged high-dose corticosteroids which can also cause hypertension and PRES. Please see sections 8.2.3.5 for further discussion related to incidences and analyses PRES as an adverse event.

8.2.3.3 Dropouts and/or Discontinuations Due to Adverse Effects

The incidence of treatment emergent adverse events leading to carfilzomib discontinuation are described in **Table 13** pooled for the B-cell ALL and T-cell ALL cohorts.

Table 13: All adverse events leading to carfilzomib dose reduction, interruption and discontinuation

	Total (N=115) n (%)
AEs leading to discontinuation of carfilzomib	33 (28.7)
AEs leading to dose reduction of carfilzomib	7 (6.1)
AEs leading to dose interruption of carfilzomib	27 (23.5)
Fatal adverse event	20 (17.4)

Source: Summation of data in Summary of clinical safety (SCS) Tables 12 and 14

There were significant adverse events leading to carfilzomib discontinuation, dose reduction, and interruption. There were 17.4% of patients that experienced fatal AEs that were contributed to combination of carfilzomib with chemotherapy. However, this incidence is consistent with that noted in patients treated with intensive chemotherapy in the relapsed/refractory ALL. There was also increased incidence (28.7%) of carfilzomib discontinuation than expected in the present study suggesting poor tolerability of this combination but given this was a single-arm study, the contribution of carfilzomib was not feasible. The higher rate of discontinuation could have also impacted efficacy.

8.2.3.4 Significant Adverse Events

Table 14: Incidence of Grade 3 or higher treatment emergent adverse events (TEAE) of 5 or more patients by preferred for the safety population

Preferred term	Total (N=115) n (%)
Anemia	51 (44.3)
Thrombocytopenia	32 (27.8)
Neutropenia	30 (26.1)
Febrile neutropenia	29 (25.2)
Leukopenia	22 (19.1)
White blood cell count decreased	16 (13.9)
Hypokalemia	16 (13.9)
Platelet count decreased	16 (13.9)
Alanine aminotransferase increased	15 (13.0)
Hypertension	14 (12.2)
Neutrophil count decreased	11 (9.6)
Septic shock	9 (7.8)
Aspartate aminotransferase increased	8 (7.0)
Lymphopenia	8 (7.0)
Sepsis	8 (7.0)
Tumor lysis syndrome	7 (6.1)
Posterior reversible encephalopathy syndrome	5 (4.3)
Hyperglycemia	5 (4.3)
Lymphocyte count decreased	5 (4.3)
Pneumonia	5 (4.3)
Hypophosphatemia	5 (4.3)

Source: Summation of data in SCS Tables 20 and 22

The significant adverse events noted in Study 1 for B-cell and T-cell ALL cohorts are consistent with those expected for patients receiving intensive cytotoxic chemotherapy regimen. There was a slightly higher incidence (4.3%) of severe PRES during the conduct of this study than what is reported in the published literature for chemotherapy backbone. PRES is a known to be associated with carfilzomib use in adults being treated with multiple myeloma.

8.2.3.5 Treatment Emergent Adverse Events and Adverse Reactions

Treatment-emergent adverse events (TEAE) of interest (any grade) were analyzed for both B-cell and T-cell ALL cohorts together based on known safety profile of carfilzomib from adult patients. The most common (≥ 10%) TEAE of interests are described in **Table 15**.

Table 15: TEAE of interest based on known safety profile of carfilzomib with ≥10% incidence

Preferred term	B-cell ALL (N=67) n (%)	T-cell ALL (N=48) n (%)	Total (N=115) n (%)
Acute renal failure	7 (10.4)	6 (12.5)	13 (11.3)
Cardiac arrhythmias	7 (10.4)	2 (4.2)	9 (7.8)
Hematopoietic leukopenia	47 (70.1)	31 (64.6)	78 (67.8)
Hematopoietic thrombocytopenia	36 (53.7)	25 (52.1)	61 (53.0)
Hemorrhage	19 (28.4)	16 (33.3)	35 (30.4)
Hepatic disorders	37 (55.2)	26 (54.2)	63 (54.8)
Hypertension	30 (44.8)	15 (31.3)	45 (39.1)
Infusion reaction	31 (46.3)	25 (52.1)	56 (48.7)
Respiratory tract infection	20 (29.9)	16 (33.3)	36 (31.3)
Reversible posterior leukoencephalopathy syndrome	9 (11.9)	7 (14.6)	16 (13.9)
Tumor lysis syndrome	8 (11.9)	4 (8.3)	12 (10.4)
Vascular hypotensive disorders	5 (7.5)	8 (16.7)	13 (11.3)

Source: Summation of data in SCS Tables 32 and 34

The high incidences of hematopoietic leukopenia and thrombocytopenia were as expected for patients being treated with cytotoxic therapies. As noted, the incidence of PRES was higher than expected (13.9%) in this study which is possibly added effects of carfilzomib and prolonged high-dose corticosteroids use. In the published literature, PRES incidence in pediatric ALL during induction is expected to be much lower (1.8%) (Kiermasz et al 2023). Carfilzomib safety profile does have PRES as an identified risk. The mechanism of action of PRES related to carfilzomib is not known. In the most recent postmarketing risk-benefit report, the Applicant reported that PRES incidence in pooled safety data from clinical studies of carfilzomib in combination with other agents used for treatment of R/R multiple myeloma (including dexamethasone) was 14.6% (95% CI: 0.99, 1.89) in 584 patients. Thus, the incidence of PRES in the current application in pediatric population is comparable to that of adult patients with multiple myeloma and potentially related to combined effects of carfilzomib and corticosteroids.

8.2.3.6 Laboratory Findings

B-cell ALL: Most patients (65, 97.0%) had at least 1 grade 3 or 4 clinical laboratory toxicity. Grade 3 laboratory toxicities in >5 patients were observed for alanine aminotransferase (17, 25.4%), potassium (16, 23.9%), aspartate aminotransferase (13, 19.4%), lymphocytes (12, 17.9%), platelets (9, 13.4%), albumin (7, 10.4%), bilirubin (6, 9.0%), sodium (7, 10.4%), and phosphorus (6, 9.0%). Grade 4 laboratory toxicities in >5 subjects were observed for total neutrophils (56, 83.6%), platelets (53, 79.1%), and lymphocytes (47, 70.1%).

T-cell ALL: All patients (48, 100.0%) had at least 1 grade 3 or 4 clinical laboratory toxicity. Grade 3 laboratory toxicities in >5 subjects were observed for alanine aminotransferase (17, 35.4%), lymphocytes (15, 31.3%), platelets (11, 22.9%), potassium (14, 29.2%), aspartate

aminotransferase (9, 18.8%), bilirubin (8, 16.7%), and phosphorus (6, 12.5%). Grade 4 laboratory toxicities in >5 subjects were observed for total neutrophils (42, 87.5%), platelets (33, 68.8%), lymphocytes (25, 52.1%), and glucose (7, 14.6%).

The changes in laboratory parameters noted above across both the B-cell ALL and T-cell ALL cohort are consistent with those that are noted for patients receiving cytotoxic chemotherapy. No new parameters were identified.

8.2.4 Analysis of Submission-Specific Safety Issues

No submission-specific safety issues were identified.

8.2.5 Safety in the Postmarket Settings

8.2.5.1 Safety Concerns Identified Through Postmarket Experience

The Applicant submitted last periodic benefit-risk evaluation report on September 26, 2024, encompassing reporting period from July 20, 2023, to July 19, 2024. Safety surveillance and evaluation mechanism entailed reviewing aggregates of adverse event data from clinical studies and postmarketing experience. Two new safety signals were identified and closed during the reported period. Hypersensitivity reactions and angioedema were identified by the FDA and the Applicant conducted a review using their clinical database. Out of 326,084 patients exposed to carfilzomib, 24 hypersensitivity events and 25 angioedema events were identified with estimated incidences of 0.007% (24/326,084) and 0.008% (25/326,084), respectively. These AEs were considered likely infusion related reactions (IRRs) rather than hypersensitivity reactions related to carfilzomib. Another safety signal identified during the most recent reporting period was fatal cardiac events in pediatric patients related to a 4-year-old female patient with ALL who received carfilzomib during the conduct of Study 1 from this current application. An aggregate review of safety data was performed by the Applicant related to all cases of cardiac events found 2 fatal and 3 nonfatal events. One fatal event was cardio-respiratory arrest associated with sepsis secondary to infection and concomitant renal and liver dysfunction. The second fatal event was of cardiac arrest related to ALL progression. Nonfatal cardiac events were characterized as angina pectoris, pulmonary edema, and cardiomyopathy. However, there was no causation determined between carfilzomib administration and cardiac events. Furthermore, there were no increased cardiac related AEs noted in the study submitted within this application. No new safety signals were determined during the most recent benefit-risk evaluation report and the benefit-risk remains unchanged.

8.2.6 Integrated Assessment of Safety

Patients with R/R ALL treated with intensive chemotherapy backbone (VXLD) used in the treatment arm in combination with carfilzomib in Study 20140106 can lead to myelosuppression, laboratory abnormalities, and infections during the course of the treatment.

These effects can be secondary to the underlying active disease, cytotoxic nature of backbone chemotherapy agents, or the addition of carfilzomib. While the external control arm provided a way to compare contributions of carfilzomib for efficacy evaluation, its comparison with the treatment arm to isolate safety and tolerability of carfilzomib versus the chemotherapy backbone was not possible. Based on the review of the CSR of the safety analysis dataset of all patients that received carfilzomib in combination with VXLD chemotherapy, there were no new safety signals that were identified that could be directly contributed to carfilzomib.

There were two notable findings during the safety review that are important to highlight. There was an increased incidence of any grade PRES (13.9%) noted in the safety population. While the incidence of PRES is higher than induction chemotherapy alone (1.8%), PRES is a known adverse event of carfilzomib in combination with therapies used to treat multiple myeloma in adults, where incidence is 14.6%. Thus, PRES incidence was comparable. Second notable issue was the increased incidence of deaths in the B-cell ALL cohort compared to the T-cell ALL cohort. However, pediatric patients with multiple relapsed treated with intensive chemotherapy have increased risk of fatal outcomes compared to newly diagnosed patients. B-cell ALL cohort had more patients that were multiply relapsed compared to T-cell ALL cohort.

We conclude that treating pediatric patients with R/R B-cell ALL and T-cell ALL with multiagent chemotherapy backbone and carfilzomib showed a safety profile that was expected or already known for carfilzomib and no new signals or increased incidences of known safety concerns were identified.

8.3 Statistical Issues

The effectiveness of carfilzomib in combination with VXLD chemotherapy backbone for R/R B-cell and T-cell ALL is not established in the submitted studies. The primary efficacy comparison is based on the IPTW adjusted CR rate at the end of induction therapy between Study 1 and a contemporary external control from Study 2. This comparison shows that it does not have significant superiority over the VXLD chemotherapy backbone for either B-cell (14.8% [95% CI: 5.9%, 23.7%] versus 7.8% [95% CI: 1%, 14.7%]) or T-cell (13.6% [95% CI: 3.5%, 23.8%] versus 9.1% [95% CI: 0.7%, 17.5%]) ALL patients, resulting in both 95% CIs of odds ratio containing the threshold of 1 (i.e., 2.039 [95% CI: 0.543, 7.658] for B-cell and 1.580 [95% CI: 0.470, 5.308] for T-cell).

The presented study results should be interpreted with several limitations. First, this is a comparison of a single-arm cohort versus an external control arm rather than a concurrent randomized comparison and therefore has some inherent potential influence of confounders and unmeasured biases. The patient populations have some key differences that could have impacted the study outcomes. For example, the majority of patients in Study 1 are enrolled outside of the US, versus the majority of patients in Study 2 are enrolled in the US and Australia, which could lead to heterogeneity of prior therapy, subsequent therapy, and supportive care standards.

The Applicant addresses the above-mentioned differences in the treatment groups by the propensity score method which is usually used for clinical situations in which randomized trials are not feasible. Although there are distinct advantages to using propensity scores, there are also limitations. It is important to note that propensity score methods work best in large datasets in which one can obtain a reasonable spread of baseline characteristics between the treatment groups. Furthermore, the quality of the propensity score analysis is dependent on adequate specification of the propensity score model. The propensity score will only adjust for the impact of observed confounders that are included as predictors in the logistic regression used to generate it. There will be no adjustment for the impact of baseline characteristics that are not included in the propensity score model, including unknown or unmeasured covariates. In the submitted external control data, some key prognostic factors used in the propensity score model are missing; for example, relapse time from prior HSCT is missing for 88% of patients in Study 2. This lack of data would compromise the adequacy of the propensity score model.

Additionally, the assessment schedules do not align between Study 1 and 2 for response endpoints as well as time to event endpoints. For example, not all the response assessments at the end of induction in Study 2 necessarily fall in the analysis window of 29 to 45 days as specified in Study 1 because the real-world treatments in Study 2 vary widely and therapies with varying treatment cycle durations may be shorter than 29 days or longer than 45 days. The capture of long-term outcomes, such as EFS and OS, is not as frequent in Study 2 as in Study 1. This is a particular concern for the endpoint of EFS, which includes the following as events: refractory/non-response to therapy, relapse, and death. In real-world practice, patients with overt clinical symptoms of ALL often do not have a bone marrow conducted to assess response when it is obvious these patients do not have a response to therapy. These patients are not counted as an EFS event (e.g., refractory/treatment failure) and continue to be followed for EFS in Study 2. In addition to these concerns, the data collection and quality in Study 2 may not be as reliable as in Study 1 given the real-world nature of Study 2.

Lastly, carfilzomib does not have an FDA-approved adult indication for ALL from which efficacy for the pediatric population could be extrapolated.

8.4 Conclusions and Recommendations

The Applicant submitted the supplemental NDA to provide reports of pediatric studies conducted in response to PWR. The Applicant is not seeking a new indication in this submission as the submitted study did not meet its primary endpoint. The Applicant evaluated the combination of carfilzomib with chemotherapy for the treatment of pediatric R/R ALL in an externally controlled, multicenter, single-arm, open-label study. The review team concludes that the effectiveness of carfilzomib in combination with chemotherapy was not established. The safety review was not able to isolate contributions of carfilzomib alone; however, the safety findings were known and expected for patients with R/R ALL receiving intensive chemotherapy and carfilzomib. No new safety signals or increased incidences of safety issues were determined.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee or other external consultations were required for the current application.

10 Pediatrics

This supplemental NDA was not for a new indication or other PREA trigger, so PREA does not apply.

Studies 20140106 and 20180065 were the subject of a Pediatric Written Request (PWR) issued under BPCA. FDA agrees that the terms of the PWR were met. Review by the pediatric exclusivity board granted Pediatric Exclusivity. See the annotated response to the PWR for details on the review of the fulfillment of the PWR.

11 Labeling Recommendations

11.1 Prescribing Information

The initial proposed edits to Section 8.4 Pediatric Use by the applicant are as follows:

(b) (4)

Upon review by the FDA, the following changes were proposed by FDA:

- A description of the trial design was added to follow the recommendations found in Guidance for Industry – Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling March 2019, which states "when the data from negative or inconclusive pediatric studies suggest clinically significant differences in responses (e.g., adverse reactions, pharmacodynamic/pharmacokinetic data) in pediatric patients (either all pediatric patients or in specific pediatric age group(s)) compared with adults, a summary of this information should be included in the Pediatric Use subsection."
- FDA recommended adding NCT numbers to provide additional information for providers.
- The age range from 1 to <17 years was added based on 21 CFR 201.57(c)(9)(iv) that states "The terms pediatric population(s) and pediatric patient(s) are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents."
- The FDA included a description of the PK parameters in pediatric patients to provide additional information to healthcare providers.

The applicant agreed with FDA's proposed changes and subsection 8.4 Pediatric Use now includes the following:

The safety and effectiveness of Kyprolis in pediatric patients have not been established.
The safety and effectiveness of Kyprolis in combination with chemotherapy was evaluated, but not established in an open label trial (Study 20140106; NCT02303821) in 124 patients aged 1 to younger than 17 years with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) who have received prior targeted B-cell immune therapy or relapsed or refractory T-cell ALL.

No new safety signals were observed in these pediatric patients. The systemic exposure of carfilzomib in these pediatric patients was within range of that observed in adults given the same dose based on body surface area.

11.2 Patient Labeling

Not applicable.

12 Risk Evaluation and Mitigation Strategies (REMS)

No new concerning safety signals were noted, and the existing safety issues are adequately managed through the agreed upon product labeling.

13 Postmarketing Requirements and Commitments

None.

14 Appendices

14.1 Pharmacometrics Review

14.1.1 Population PK analysis

14.1.1.1 Review Summary

In general, the applicant's population PK (PopPK) analysis is considered acceptable for the purpose of characterizing the PK profile of carfilzomib in pediatric patients with relapsed or refractory acute lymphoblastic leukemia (ALL). Kyprolis (carfilzomib) was approved to treat adult patients with [redacted] (b) (4) on July 20, 2012. In the current submission, the effectiveness of carfilzomib in combination with chemotherapy was evaluated in Study 20140106, but not established for patients aged 1 to younger than 21 years, with relapsed or refractory ALL. The applicant is not seeking an indication change to the label. Section 8.4 (S19) "Pediatric Use" of the U.S. Prescribing Information (USPI) will be updated to include the information from Study 20140106.

In the current review cycle, the PopPK report was updated based on our Information Request (IR) on February 7, 2025, to include pediatric patients <17 years old. Based on the PopPK model and simulation result, the AUC and Cmax at cycle 1 day 8 (C1D8) for subjects receiving 56 mg/m^2 dose are comparable between adult and pediatric patients. The updated results are acceptable**.**

Table 16: Specific Comments on Applicant's Final Population PK model

Utility of the final model			**Reviewer's Comments**
Support applicant's proposed labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	<u>Change in current supplement:</u> The applicant did not propose any change of label related to intrinsic factor in current supplement. The following language was added in Section 8.4 "Pediatric Use". [redacted] (b) (4)	Based on the PopPK model and simulation result, the AUC and Cmax at cycle 1 day 8 (C1D8) are comparable between adult and pediatric patients (geometric least square mean ratio ~1.2, adult/pediatric).

	Extrinsic factor	N/A	N/A

14.1.1.2 Introduction

The primary objectives of applicant's analysis were to:

- Evaluate the impact of subjects' demographics as predictors of pharmacokinetic variability.
- Compare the PK of pediatric subjects with that of adults.
- Predict individual exposure metrics of pediatric subjects to be used in subsequent exposure-response analyses.

14.1.1.3 Model development

Data

PopPK analysis was performed using available clinical data from the pooled adult and pediatric dataset from nineteen Phase 1, 2 and 3 studies, including 18 clinical studies with adult patients with multiple myeloma or solid tumors (PX-171-001, PX-171-002, PX-171-003 – Part 2 (A1), PX-171-004, PX-171-005, PX-171-006, PX-171-007, PX-171-009, CFZ001, CFZ002, 2011-003 (ENDEAVOR), 2012-002 (CHAMPION), 20140242, 20140355 (ARROW), 20160275 (CANDOR), and MMY1001). The pooled dataset contained 10862 plasma concentrations of carfilzomib from 1906 subjects. In original analysis, 763 plasma concentrations were from 134 pediatric subjects in Study 20140106 (Age < 21 years old). Per the Agency's IR comment regarding pediatric subject age cutoff (1 to <17), 16 subjects from the pediatric study 20140106 which were ≥17 years at enrollment were excluded from the pediatric population and instead pooled with the adult population.

Brief descriptions of the studies included are presented in **Table 17**.

Table 17: Summary of Studies with PK Sampling Included in Population PK Analysis

	Amgen Study #	Phase	Subjects with PK	# PK samples	Population	Description	Carfilzomib Dosing	PK Sampling
1	20130401 (CFZ001)	1	26	348	Relapsed MM and end stage renal disease	Phase 1, open-label, single-arm study of the pharmacokinetics and safety of carfilzomib in subjects with relapsed multiple myeloma and end-stage renal disease	30 min IV infusion 28-day treatment cycles; Cycle 1: 20 mg/m^2 IV on Days 1 and 2, escalation to 27 mg/m^2 on Days 8, 9, 15, and 16; Cycles 2+: 56 mg/m^2 on Days 1, 2, 8, 9, 15, and 16	Cycle 1 Day 16 and Cycle 2 Day 1 (predose, 15 min after start of infusion, EOI, 5, 15, and 30 min, and 1, 2, 4h after EOI)
2	20130402 (CFZ002)	1	34	403	Advanced malignancies and hepatic impairment	Phase 1, open-label, single-arm study of the pharmacokinetics and safety of carfilzomib in subjects with advanced malignancies and varying degrees of hepatic impairment	30 min IV infusion 28-day treatment cycles Cycle 1: 20 mg/m^2 IV on Days 1 and 2, followed by escalation to 27 mg/m^2 on Days 8, 9, 15, and 16 Cycles 2+: 56 mg/m^2 on Days 1, 2, 8, 9, 15 and 16	Cycle 1 Day 16 and Cycle 2 Day 1 (predose, 15 min a start of infusion, EOI, 5, 15, and 30 min, and 1, 2, 4 h after EOI)
3	20130403 (2012-002, Champion)	1/2	27	446	Progressive MM	A Phase 1/2 Study of Weekly Carfilzomib in Combination with Dexamethasone for Progressive Multiple Myeloma	30 min IV infusion 28-day treatment cycles Cycle 1: 20 mg/m^2 IV on Days 1. All subsequent carfilzomib doses (45, 56, 70, or 88 mg/m^2) will be administered according to the dose assignment for each cohort	Cycle 1 Day 1 and Cycle 2 Day 15 (predose, 5, 15 min after start of infusion, EOI, 5, 15, and 30 min, and 1, 2, and 4h after EOI)
4	20140117 (PX171-001)	1	27	170	Hematological malignancies	A Phase 1 Study of the Safety and Pharmacokinetics of Escalating Intravenous Doses of the Proteasome Inhibitor PR-171 in Patients with Hematological Malignancies: Two Week Cycle	This Phase 1 study was an open-label, dose-escalation safety trial with the primary objective of characterizing DLTs and identifying the MTD of carfilzomib given daily x x 5 in a 14-day cycle in subjects with previously treated hematologic malignancies.	Blood samples were collected to measure PK of carfilzomib on Cycle 1, Day 1 at pre-dose, 5, 15, and 30 minutes, 1, 2, 4, and 24 hours post-dose. On Cycle 1, Day 5, on Cycle 2, Day 1, and on Cycle 3, Day 1, blood samples were collected to measure plasma carfilzomib at pre-dose and 30 minutes post-dose
5	20140118 (PX171-003)	2	107	246	R/R MM	Phase 2, open-label single-arm study of single-agent carfilzomib in subjects with relapsed and refractory multiple myeloma	2–10 min IV infusion 28-day treatment cycles; Dose escalation following Cycle 1 for A1 study: 20 mg/m^2: Cycle 1, Days 1, 2, 8, 9, 15 and 16; 27 mg/m^2: Cycles 2+, Days 1, 2, 8, 9, 15, and 16	Cycle 1 Day 1 (predose, ~15 min postdose); Cycle 1 Day 8 (~30 min postdose); Cycle 2 Day 15 (30–60 min postdose)
6	20140119 (PX171-004)	2	52	110	R/R MM	Phase 2, open-label, single-arm study of single-agent carfilzomib in subjects with relapsed and/or refractory multiple myeloma who are bortezomib-naïve and who have been previously treated with bortezomib	2–10 min IV infusion 28-day treatment cycles, All bortezomib-exposed subjects and one cohort of bortezomib-naïve subjects received 20 mg/m^2 on Days 1, 2, 8, 9, 15, and 16 in all Cycles. The remaining bortezomib-naïve subjects escalated from a starting dose of 20 mg/m^2 to a target dose of 27 mg/m^2 after Cycle 1.	Cycle 1 Day 1 (predose, ~15 min postdose); Cycle 1 Day 8 (~30 min postdose) Cycle 2 Day 15 (30-60 min postdose)
7	20140122 (PX171-002)	1	36	276	Hematological malignancies	A Phase I Study of the Safety and Pharmacokinetics of Escalating Intravenous Doses Patients with Hematological Malignancies: four week cycle	Escalating dose levels of carfilzomib administered on 2 consecutive days per week for 3 weeks, followed by 1 week of rest, in 4-week cycles. The starting dose of carfilzomib was 1.2 mg/m^2 and was to advance to 27 mg /m^2	Predose, 5, 15, and 30 minutes, and at 1, 2, and 4 hours after carfilzomib administration on Day 1 Cycle 1; on Days 2 and 8, and in Cycle 2 on Day 1 at pre-dose and at 30 minutes post dose.
8	20130393 (PX171-007)	1b/2	73	970	Relapsed solid tumors, MM, Lymphoma	Phase 1b/2, multicenter open-label study of the safety and activity of carfilzomib in subjects with relapsed solid tumors, multiple myeloma or lymphoma	2–10 min or 30-min IV infusion 28-day treatment cycles, up to 12 cycles Three treatment cohorts: 20 mg/m^2: All days 20/27 mg/m^2: 20 mg/m^2 Days 1 and 2 of Cycle 1, 27 mg/m^2 thereafter 20/36 mg/m2: 20 mg/m^2 Days 1 and 2 of Cycle 1, 36 mg/m^2 thereafter	Cycle 1 Days 1 and 16; Cycle 3 Days 1 and 16; Cycle 5 Days 1 and 16 (predose, EOI, 5, 15 and 30 min, 1, 2, and 4 h postdose)

	Amgen Study #	Phase	Subjects with PK	# PK samples	Population	Description	Carfilzomib Dosing	PK Sampling
9	20130395 (PX171-009, Aspire)	3	110	573	R/R MM	Phase 3, multicenter randomized study comparing carfilzomib, lenalidomide, and dexamethasone (CRd) versus lenalidomide and dexamethasone (Rd) in subjects with relapsed multiple myeloma	2–10 min IV infusion 28-day treatment cycles, up to 18 cycles 20/27 mg/m^2: 20 mg/m^2 on Days 1 and 2 of Cycle 1; 27 mg/m^2 on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 of Cycle 2–12. Cycles 13-18: 27 mg/m^2 on Days 1, 2, 15, and 16	Cycle 1 Days 1 and 8; Cycle 2 Day 15 (predose, ~15 min postdose and 15 min to 3 h postdose)
10	20130398 (2011-003, Endeavor)	3	135	836	R/R MM	Randomized, open label, multicenter study of subjects with relapsed multiple myeloma (1 to 3 prior lines) randomized 1:1 to treatment with either carfilzomib and dexamethasone (Kd) or bortezomib and dexamethasone (Vd)	30 min IV infusion 28-day treatment cycles Cycle 1: 20 mg/m^2 IV on Days 1 and 2, followed by escalation to 56 mg/m^2 on Days 8, 9, 15, and 16 Cycles 2+: 56 mg/m^2 Dexamethasone 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23	Cycle 1: Day 1 (EOI, 10 min post-infusion) Day 2 (predose, 20 min postdose) Day 8 (EOI, 10, 60–75, and 80–95 min post-infusion)
11	20140120 (PX171-005)	2	43	807	R/R MM with renal impairment	Carfilzomib in multiple myeloma subjects with renal impairment: pharmacokinetics and safety	2–10 min IV infusion 28-day treatment cycles, up to 12 cycles Days 1, 2, 8, 9, 15, and 16 Cycle 1: 15 mg/m^2 Cycle 2: Escalation to 20 mg/m^2 Cycle 3+: 27 mg/m^2	Cycle 1 Days 1 and 15; Cycle 2 Day 15 (predose, EOI, 5, 15 and 30 min, 1.0, 1.5, 2, 4, 6, and 24 h postdose) 24 h samples to be drawn prior to next scheduled dose
12	20140121 (PX171-006)	1b	38	163	R/R or progressive MM	Phase 1b dose-escalation study of carfilzomib, lenalidomide, and low-dose dexamethasone in subjects with relapsed or progressive multiple myeloma	2–10 min IV infusion 28-day treatment cycles: 3 weeks ON/1 week OFF Cycles 1–12: Days 1, 2, 8, 9, 15, and 16 Cycles 13+: Days 1, 2, 15, and 16 Cohorts 1–3: 15 mg/m^2 Cohorts 4–5: 20 mg/m^2 Cohort 6: 27 mg/m^2	Cycle 1: Day 1 (predose, 15 mins postdose, 15min – 3h postdose) Cycle1 Day 2 and Cycle 2 Day 15: (15 min postdose, 15 min – 3 h postdose)

	Amgen Study #	Phase	Subjects with PK	# PK samples	Population	Description	Carfilzomib Dosing	PK Sampling
13	20140355 (CFZ2014, Arrow)	3	88	237	R/R MM	A Randomized, Open-label, Phase 3 Study Carfilzomib in Combination with Dexamethasone, Comparing Once-weekly versus Twice-weekly Carfilzomib Dosing	30 min IV infusion 28-day treatment cycles **Arm A: Once-weekly •** Carfilzomib 20 mg/m^2 Cycle 1 Day 1, 70 mg/m^2 Days 8 and 15 (Cycle 1); Carfilzomib 70 mg/m2 Days 1, 8, and 15 (Cycles 2+) **Arm B: Twice-weekly •** Carfilzomib 20 mg/m^2 on Days 1 and 2 (Cycle 1), 27 mg/m^2 on Days 8, 9, 15, and 16 (Cycle 1); 27 mg/m^2 on Days 1, 2, 8, 9, 15, and 16 (Cycles 2+)	Cycle 1 Day 15
14	20140242	3	24	318		A phase 3, multicenter, open-label, single-arm study in China designed to evaluate the efficacy and safety of carfilzomib at a dose of 20/27 mg/m^2 given in combination with dexamethasone	Carfilzomib was administered as an intravenous (IV) infusion over 30 (± 5) minutes on days 1, 2, 8, 9, 15, and 16 in 28-day cycles. The carfilzomib dose was 20 mg/m^2 on cycle 1 days 1 and 2 followed by 27 mg/m^2 thereafter.	Pharmacokinetic samples were collected from 24 subjects (19 subjects with full pharmacokinetic samples [ie, cycle 1 day 1 and cycle 2 day 1] and an additional 5 subjects with cycle 1 data only)
15	20160275 (Candor)	3	445	2328	R/R MM	A Randomized, Open-label, Phase 3 Study Comparing KdD to Kd	30 min IV infusion twice weekly, on days 1, 2, 8, 9, 15, and 16. The dose was 20 mg/m^2 on cycle 1 days 1 and 2 and 56 mg/m^2 beginning on cycle 1 day 8 and thereafter.	Carfilzomib PK was collected on Cycle 1 day 8 and cycle 3 day 1
16	20190252 (MMY1001)	1	10	52	R/R MM	open-label, multi-cohort, multicenter, phase 1b study evaluating the safety and tolerability of KdD 20/70 mg/m^2 once-weekly	Days 1, 8, and 15 (± 1 day) of each 28-day cycle; 20 mg/m^2 on cycle 1 day 1 and 70 mg/m^2 beginning on cycle 1 day 8 and thereafter.	Predose, EOI on day 1 of cycles 1 to 4; additional samples were collected on cycle 2 day 1 at 0.5, 1, 2, and 4 hours after EOI

	Amgen Study #	Phase	Subjects with PK	# PK samples	Population	Description	Carfilzomib Dosing	PK Sampling
17	20140241 (CFZ0013)	1b	94	363	R/R MM and NDMM	An open-label, multicenter, Phase 1b, dose-finding study of once weekly KRd	Dose evaluation cohort 1 and dose expansion arm 3: 20 mg/m^2 C1D1; 56 mg/m^2 C1D8 and C1D15; and Cycle 2+; Dose evaluation cohort 2, dose expansion arms 1 and 2: 20 mg /m^2 C1D1; 70 mg /m^2 C1D8 and C1D15; and Cycle 2+; Dose evaluation cohort 4: 20 mg/m2 C1D1; 56 mg/m^2 on C1D8, C1D15; 70 mg/m^2 Cycle 2+	Day 8 of Cycle 1: predose, 15 minutes after the start of the infusion, immediately prior to (within 2 minutes before) the end of the infusion, and 15 and 60 minutes after the end of the infusion
18	20180015 (Arrow2)	3	403	1453	R/R MM	Randomized, open label Ph3 study comparing 20/27 BIW and 20/56 QW dosing of KRd	**Once weekly arm:** 30 min IV infusion Cycle 1: 20 mg/m^2 on day 1; 56 mg/m^2 on days 8, 15; Cycles 2-12: 56 mg/m^2 each dosing day **Twice weekly arm:** 10 min IV infusion; Cycle 1: 20 mg/m^2 on days 1 and 2, 27 mg/m^2 on days 8, 9, 15, 16; Cycles 2-12: 27 mg/m2 on each dosing days	**Sparse sampling:** C2D1 (pre-dose, 15 min after start of infusion for QW arm, EOI, 30 min post EOI) **Intensive sampling:** C1D1 (pre-dose, EOI), C1D8 (pre-dose, 15 min after start of infusion for QW arm, EOI, 15, 60, and 120 mins post EOI); C2 Days 1 and 8 (pre-dose, EOI, 60 min post EOI)
19	20140106 (CFZ008)	1b/2	134	763	Pediatrics under age 21 with R/R ALL	Phase 1b/2 study of Carfilzomib in combination with induction chemotherapy in children and young adults under age 21 with relapsed or refractory acute lymphoblastic leukemia	30 min IV infusion **Induction cycle:** Phase 1b: Carfilzomib 20 mg/m^2 day 1, target dose (20, 27, 36, 45, 56, or 70 mg/m^2) on days 2, 8, 9, 15, 16; Phase 2: Carfilzomib 20 mg/m^2 day 1, 56 mg/m^2 on days 2, 8, 9, 15, 16; **Optional Consolidation cycle:** Assigned target dose in Ph1b and 56 mg/m^2 in Ph2) on days 1, 2, 8, 9, 15, 16	Day 1: predose, EOI; Day 8: predose, 15 min after the start of infusion, EOI; and 15, 60, and 120 min after EOI

K/CRd = Kyprolis/carfilzomib, lenalidomide, and dexamethasone; EOI = end of infusion; IV – intravenous; min = minutes; Rd = lenalidomide and dexamethasone; MM = multiple myeloma, R/R = relapsed/refractory, ALL = acute lymphoblastic leukemia

Source: Table 1 in PopPK report, Population Pharmacokinetics of Carfilzomib in Adult Subjects with Multiple Myeloma and Solid Tumor Malignancies and Pediatric Subjects with Relapsed or Refractory Acute Lymphoblastic Leukemia (Nov. 1, 2024)

PopPK analysis was conducted via nonlinear mixed effects modelling with a qualified installation of the nonlinear mixed effects modelling (NONMEM) software, (Version 7.5) ((b) (4)). First-order conditional estimation with interaction (FOCEI) were evaluated. Graphical and all other statistical analyses, including evaluation of NONMEM outputs, were performed with R version 4.3.2.

Table 18 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 18: Summary of Baseline Demographic Covariates for Analysis

Covariate	Statistic	Adult (N = 1788)	Pediatric* (ages 1 to < 17years, N = 118)	Combined
AGE	Mean (SD)	63.07 (10.59)	8.37 (4.2)	59.68 (16.74)
	Median (range)	64 (17 - 89)	8 (1 - 16)	63 (1 - 89)
ALB	Mean (SD)	39.07 (5.95)	36.12 (5.44)	38.89 (5.96)
	Median (range)	40 (10 - 56)	36 (21.8 - 48)	39.95 (10 - 56)
BILI	Mean (SD)	0.01 (0.01)	0.01 (0)	0.01 (0.01)
	Median (range)	0.01 (0 - 0.1)	0.01 (0 - 0.02)	0.01 (0 - 0.1)
BSA	Mean (SD)	1.89 (0.24)	1.03 (0.34)	1.83 (0.32)
	Median (range)	1.9 (1.2 - 2.82)	1 (0.4 - 1.9)	1.88 (0.4 - 2.82)
BW	Mean (SD)	78.23 (17.58)	30.77 (15.15)	75.29 (20.86)
	Median (range)	76.2 (36 - 164.66)	26.4 (8.3 - 84.7)	75 (8.3 - 164.66)
CRCL	Mean (SD)	73.76 (48.26)	147 (59.46)	78.23 (52.04)
	Median (range)	68.2 (6.7 - 704.4)	133 (54.5 - 414.7)	70.3 (6.7 - 704.4)
PLATELT	Mean (SD)	188.73 (79.01)	90.19 (94.42)	182.61 (83.48)
	Median (range)	183 (3 - 686)	66 (0.01 - 610)	178 (0.01 - 686)
SGOT	Mean (SD)	26.23 (23.63)	56.46 (60.58)	28.08 (28.27)
	Median (range)	22 (6 - 699)	35 (8 - 419)	22 (6 - 699)
SGPT	Mean (SD)	23.14 (16.91)	70.46 (93.59)	26.09 (30.67)
	Median (range)	19 (4 - 231)	40 (5 - 780)	19 (4 - 780)
WBC	Mean (SD)	5.26 (2.91)	18.57 (42.66)	6.09 (11.42)
	Median (range)	4.8 (0.18 - 84.5)	5.22 (0.03 - 301.27)	4.8 (0.03 - 301.27)

Covariate	Value	Adult (N = 1788)	Pediatric* (ages 1 to < 17 years, N = 118)	Combined
LIVER	.	66	3	69
	1	1458	50	1508
	2	252	60	312
	3	11	5	16
	4	1	NA	1
RACE	0	51	NA	51
	1	1349	82	1431
	2	95	7	102
	3	148	14	162
	4	1	3	4
	5	1	NA	1
	6	53	NA	53
	7	9	NA	9
	8	1	NA	1
	88	79	12	91
RENAL	.	3	2	5
	1	373	100	473
	2	751	14	765
	3	580	2	582
	4	81	NA	81
SEX	Female	764	32	796
	Male	1024	86	1110

Abbreviations: ALB: Albumin, BILI: bilirubin, CRCL: creatinine clearance estimated by Cockcroft Gault formula, SGOT: aspartate transaminase, SGPT: alanine transaminase, WBC: white blood cell
** The pediatric group presented in Table 2 (d) above is based on the subjects with the age 1 to <17 years. Subjects (N=16) from the pediatric study 20140106 which were ≥17 years at enrollment were excluded from the pediatric population and instead pooled with the adult population.*

Covariate	Column name	Unit or code
Race	RACE	0 = Not provided 1 = White 2 = Black or African American 3 = Asian, ASIAN/NATIVEHAWAIIAN OR OTHER PACIFIC ISLANDER, ASIAN/PACIFIC ISLANDER 4 = American Indian or Alaskan Native 5 = Native Hawaiian or Other Pacific Islander 6 = CAUCASIAN 8 = JAPANESE 88 = Other/Multiple
Liver category	LIVER	1 = total bilirubin ≤ ULN and AST ≤ ULN 2 = total bilirubin ≤ ULN and AST > ULN 3 = ULN < total bilirubin <= 1.5 x ULN and any AST 4 = 1.5 x ULN < total bilirubin <= 3 x x ULN and any AST 5 = total bilirubin > 3 x x ULN and any AST "." = missing data
Renal category	RENAL	1=CrCL ≥ 90 mL/min 2=90 mL/min > CrCL ≥ 60 mL/min 3=60 mL/min > CrCL ≥ 30 mL/min 4=CrCL < 30 mL/min 5=End stage renal disease (hemodialysis) "." = missing data

Source: Table 2 (d) and (e) in PopPK report, Population Pharmacokinetics of Carfilzomib in Adult Subjects with Multiple Myeloma and Solid Tumor Malignancies and Pediatric Subjects with Relapsed or Refractory Acute Lymphoblastic Leukemia Table 5.NONMEM dataset variables: all covariates are included at baseline. (Feb 10, 2024).

Base model

The most recent PopPK model for carfilzomib developed in original drug approval was used as the starting point for model development. It is a two-compartment model with linear distribution to peripheral compartments, and first-order linear elimination from central compartment, with IIVs estimated for CL, V1, V2, Q, and covariate effect of BSA on CL.

Covariate analysis

Following the development of the base model, the effects of subject specific covariates on the random effects in the base structural model were explored graphically on key PK parameters. No new covariate relationship was found on any of the ETAs and therefore no further changes were expected to be made to the model. A step-wise covariate analysis was performed that considered effects of age, BSA, and sex. No additional significant covariates were obtained from this analysis.

14.1.1.4 Final Model

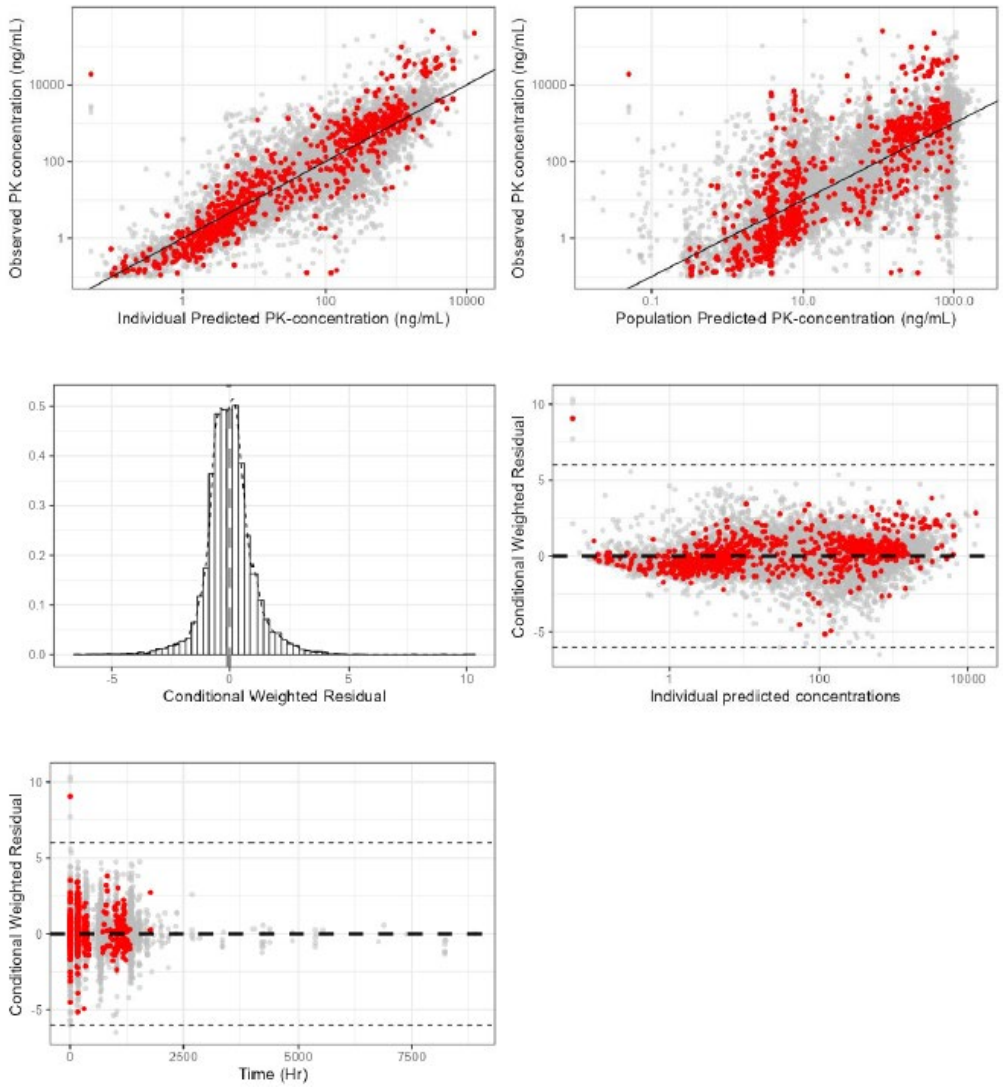
The parameter estimates for the final covariate model are listed in **Table 19**. The model described the observed data adequately, as seen in the goodness-of fit plots (**Figure 5**). Interindividual variability in most carfilzomib parameters was high (CV% > 90%), which may be result from the rapid and atypical metabolism of carfilzomib (e.g., epoxide hydrolases and peptidases).

Table 19: Parameter estimates of the final PopPK model

Parameter	Estimate	Relative standard error in estimate (%)	Interindividual variability in parameter estimate %CV
Plasma clearance, CL (L/h)	230	3.7	97
Volume of central compartment V1 (L)	22.38	4.9	105
Inter compartmental clearance, Q (L/h)	11.32	8.4	195
Volume of peripheral compartment V2 (L)	15.68	10.5	195
Exponent of BSA effect on clearance	0.52	8.9	-
SD of additive residual error on log-transformed data			
• Intensive sampling studies	1.04	0.4	-
• Sparse sampling studies	1.42	0.5	

Source: Table 4 in PopPK report, Population Pharmacokinetics of Carfilzomib in Adult Subjects with Multiple Myeloma and Solid Tumor Malignancies and Pediatric Subjects with Relapsed or Refractory Acute Lymphoblastic Leukemia (Nov. 1, 2024)

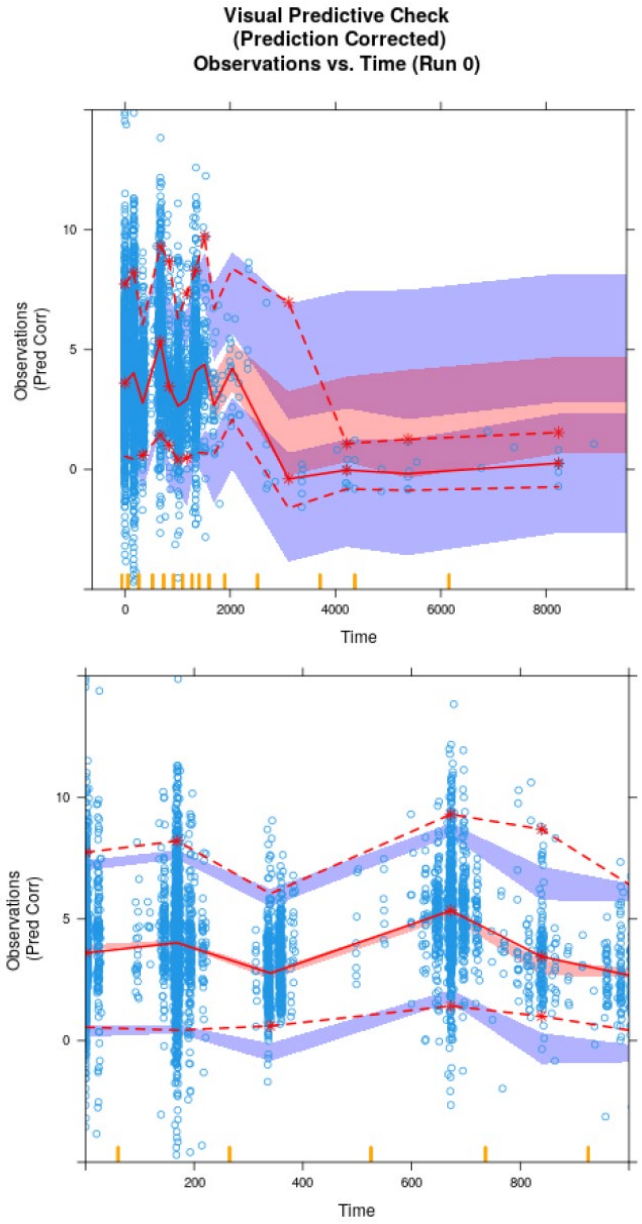
Figure 5: Goodness-of-Fit Plots for final PopPK model with combined dataset



Pediatric data from study 20140106 is shown in red.
Source: Figure 5 in PopPK report, Population Pharmacokinetics of Carfilzomib in Adult Subjects with Multiple Myeloma and Solid Tumor Malignancies and Pediatric Subjects with Relapsed or Refractory Acute Lymphoblastic Leukemia (Nov. 1, 2024)

A prediction-corrected visual predictive check (pcVPC) was performed to ensure that the model has maintained fidelity with the observed carfilzomib PK data. Model based simulations of 1000 replicates of the analysis data set were performed. Simulated and observed distributions were compared by calculating the median, 5th, and 95th percentiles for each time interval (**Figure 6**). Overall, the central tendency and the variability in pediatric patients were well captured by the PopPK model.

Figure 6: pcVPC plots for final PopPK model



The red solid line and red shaded area represent, respectively, the median of prediction-corrected observations (blue circles) and its associated 95% CI based on the simulations. The red dashed lines and blue shaded areas represent, respectively, the 5th and 95th percentiles of the prediction-corrected observations and their associated 95 CIs based on the simulations.

Source: Figure 11 in PopPK report, Population Pharmacokinetics of Carfilzomib in Adult Subjects with Multiple Myeloma and Solid Tumor Malignancies and Pediatric Subjects with Relapsed or Refractory Acute Lymphoblastic Leukemia (Nov. 1, 2024)

14.1.1.5 PK simulation based on PopPK model

Post-hoc PK parameter estimates are compared between adults and pediatric patients. Median normalized clearance, which is CL normalized by $(BSA/1.88)^a$, where a is the estimated exponent for BSA, is ~32% lower in pediatric subjects than in adults. Similarly, the volume of the plasma compartment in pediatric subjects is ~34% lower than in adults. The median terminal elimination half-life of carfilzomib in pediatric subjects is within 5% of that of adults (**Table 20**). Cmax and AUC after the dose on day 8 of cycle 1 (C1D8) are simulated for subjects receiving 56 mg/m^2 dose in both adult and pediatric populations. The simulated AUC and Cmax for the pediatric subjects overlap with that of the adults, with the geometric least square mean (GLSM) ratio for AUC and Cmax within 1.2 (adult vs Peds) (**Table 20**). The reviewer noticed that the GLSM ratio for AUC and Cmax were calculated based on "adult vs pediatric" instead of "pediatric vs adult" as described in column name. The GLSM ratio for BSA is calculated based on "pediatric vs adult".

Table 20: Comparison of PK between adults and pediatric subjects

Comparison of post-hoc PK parameter estimates from PopPK model

PK Parameter	**Adult** Median (90 percentile)	**Pediatric* (ages 1 to < 17)** Median (90 percentile)	**Ratio of pediatric* to adults** (GLSM ratio^ and 95% CI)
N	1788	118	
BSA	1.9 (1.2 - 2.82)	1 (0.4 - 1.9)	0.52 (0.49-0.55)
Plasma clearance, CL (L/hr)	210 (79 - 817)	120 (25 - 347)	0.48 (0.41-0.57)
BSA effect normalized Plasma clearance $CL/(BSA/1.88)^a$, (L/hr)	207 (79 - 803)	166 (31 - 425)	0.68 (0.58-0.79)
Volume of plasma compartment, V1 (L)	19 (10 - 84)	14 (5 - 47)	0.66 (0.58-0.75)
Half life, $t_{1/2}$ (hr)	0.99 (0.76 - 1.46)	0.94 (0.74 - 1.7)	0.99 (0.95-1.04)
BSA exponent, a = 0.516			

Comparison of model-predicted PK metrics on C1D8#

PK metric	Adult Median (90 percentile)	Pediatric* (ages 1 to < 17) Median (90 percentile)	Ratio of Pediatric* to Adult (GLSM ratio^ and 95% CI)
N	816	83	
BSA	1.88 (1.5 - 2.23)	0.9 (0.5 - 1.7)	0.52 (0.48-0.56)
AUC (C1D8) hr*ng/mL	510 (98 - 1524)	473 (196 - 3340)	1.2 (0.99-1.46)
Cmax (C1D8) ng/mL	959 (164 - 2637)	870 (308 - 4169)	1.15 (0.95-1.39)

** The pediatric group presented in Table 6 (c) above is based on the subjects with the age 1 to <17 years. Subjects (N=16) from the pediatric study 20140106 which were ≥17 years when the study was conducted were excluded from the pediatric population and instead pooled with the adult population.*

^ The reported geometric least square mean (GLSM) ratio is computed based on the ratio of means and 95% CI obtained from performing a t-test of the log-transformed parameters of the two populations.

#: The reviewer noticed the GLSM ratio for AUC and Cmax are calculated based on "adult vs pediatric" instead of "pediatric vs adult" as described in column name.

Source: Table 6 (c) and (d) in PopPK report, Population Pharmacokinetics of Carfilzomib in Adult Subjects with Multiple Myeloma and Solid Tumor Malignancies and Pediatric Subjects with Relapsed or Refractory Acute Lymphoblastic Leukemia (Feb 10, 2025)

14.1.2 Exposure-Response analysis

14.1.2.1 Review Summary

The applicant also conducted E-R analysis for clinical efficacy and safety endpoints for 140 pediatric subjects with R/R ALL who were enrolled in either the phase 1b or phase 2 portions of Study #20140106 and received carfilzomib in combination with R3 or VXLD induction chemotherapy. A separate analysis was also conducted for 129 pediatric subjects with R/R ALL from Study 20140106 (phase 1b or 2) who received carfilzomib in combination with VXLD induction chemotherapy. Subjects received carfilzomib as a 30-minute IV infusion at planned target dose levels ranging from 15 to 56 mg/m^2.

The efficacy endpoints analyzed were overall response rate (Composite CR: CR + CRh + Cri + CRp), overall survival (OS), and duration of response (DOR). A bottom-up mechanistic PK/PD model was used to predict proteasomal inhibition in pediatric subjects in Study #20140106. For safety endpoints, an analysis was performed in the same 140 subjects. The safety endpoints included any grade adverse events leading to carfilzomib discontinuation, any grade 3 or higher adverse events, and cardiac- and hepatic/renal-related adverse events.

As the applicant doesn't plan to pursue pediatric usage, the ER analysis result is briefly summarized as below.

ER analyses for efficacy showed a flat relationship between carfilzomib exposure (AUC and C_{max}) and the rate of CR or composite CR at the end of the induction cycle. No differences in exposure-efficacy relationships were observed between pediatric subjects with B-cell versus T-cell ALL. A flat relationship was also seen between carfilzomib exposure and proteasome inhibition at the end of the induction cycle based on PK/PD model analysis.

The ER safety analysis with the T-cell ALL population having marginally significant exposure-response curve for Infection vs $C_{max.peak}$ (p value = 0.02), and the B-cell ALL population having marginally significant curve for Lymphopenia (Grade = 3) vs $C_{max.peak}$ (p value = 0.03). In subjects who received VXLD chemotherapy, the ER for patients with T-cell ALL and B-cell ALL look similar (no relationship, p value > 0.05) for all safety endpoints, except for Neutropenia vs $AUC._{C1avg}$ in the B-cell ALL population which has p value = 0.02.

Overall, given the high inter-individual variability (>90%) in the PopPK data that was used to fit the model and generate the exposure estimates for the ER analysis, the ER result should only be considered as supportive evidence.

14.2 References

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NDA Multi-disciplinary Review and Evaluation
NDA 202714 SE8-036 KYPROLIS (carfilzomib) for injection
Signatures

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Keng Hee Peh, PharmD, PhD	OCP/DCPI	Sections: 6, 14.1	☒ Authored ☐ Approved
	Signature: KENG HEE PEH -S Digitally signed by KENG HEE PEH -S Date: 2025.05.19 22:03:46 -04'00'			
Master Clinical Pharmacology Reviewer	Xiling Jiang, PhD	OCP/DCPI	Sections: 6, 14.1	☒ Authored ☒ Approved
	Signature: Xiling Jiang -S Digitally signed by Xiling Jiang -S Date: 2025.05.20 08:33:02 -04'00'			
Pharmacometrics Reviewer	Yun Wang, PhD	OCP/DPM	Sections: 6, 14.1	☒ Authored ☐ Approved
	Signature: YUN WANG -S Digitally signed by YUN WANG -S Date: 2025.05.20 08:36:27 -04'00'			
Pharmacometrics Team Leader	Jiang Liu, PhD	OCP/DPM	Sections: 6, 14.1	☒ Authored ☒ Approved
	Signature: JIANG LIU -S Digitally signed by JIANG LIU -S Date: 2025.05.20 08:58:04 -04'00'			
Division Director	Brian Booth, PhD	OCP/DPM	Sections: 6, 14.1	☐ Authored ☒ Approved
	Signature: BRIAN P. BOOTH -S Digitally signed by BRIAN P. BOOTH -S Date: 2025.05.20 10:34:46 -04'00'			
Clinical Reviewer	Mansi Dalal, MD	OOD/DHMI	Sections: 1, 2, 3, 7, 8, 10, 11	☒ Authored ☐ Approved
	Signature: MANSI S. DALAL -S Digitally signed by MANSI S. DALAL -S Date: 2025.05.21 08:25:36 -04'00'			
Clinical Team Leader	Lori Ehrlich, MD, PhD	OOD/DHMI	Sections: 1, 2, 3, 7, 8, 10	☒ Authored ☒ Approved
	Signature: Lori Ehrlich -S Digitally signed by Lori Ehrlich -S Date: 2025.05.22 08:26:57 -04'00'			

NDA Multi-disciplinary Review and Evaluation
NDA 202714 SE8-036 KYPROLIS (carfilzomib) for injection
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DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
Statistics Reviewer	Xin Wang, PhD	OB/DBIX	Sections: 8	☒ Authored ☐ Approved
	Signature: Xin Wang -S Digitally signed by Xin Wang -S Date: 2025.05.21 09:26:34 -04'00'			
Statistical Team Leader	Jonathon Vallejo, PhD	OB/DBIX	Sections: 8	☐ Authored ☒ Approved
	Signature: JONATHON J. VALLEJO -S Digitally signed by JONATHON J. VALLEJO -S Date: 2025.05.21 09:34:16 -04'00'			
Associate Director for Labeling (ADL)	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	☐ Authored ☒ Approved
	Signature: Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S Date: 2025.05.21 09:07:00 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Lori Ehrlich, MD, PhD	OOD/DHMI	Sections: All	☐ Authored ☐ Approved
	Signature: *{See appended electronic signature page}*			
Deputy Division Director	Kelly Norsworthy, MD	OOD/DHMI	Sections: All	☐ Authored ☐ Approved
	Signature: *{See appended electronic signature page}*			

DBIX: Division of Biometrics IX; DCPI: Division of Cancer Pharmacology I; DHMI: Division of Hematologic Malignancies I; DPM: Division of Pharmacometrics; OB: Office of Biostatistics; OCP: Office of Clinical Pharmacology; OOD: Office of Oncologic Diseases

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/s/

LORI A EHRLICH
05/22/2025 12:57:32 PM

KELLY J NORSWORTHY
05/22/2025 02:32:58 PM