Office of Clinical Pharmacology Review

NDA Numbers	207103 S-023 (capsules)/SDN 2258 212436 S-011 (tablets)/SDN 2201
Link to EDR	\\CDSESUB1\EVSPROD\nda207103\1751 \\CDSESUB1\EVSPROD\nda212436\0849
Applicant	Pfizer
Submission Date	03/17/2025
Submission Type	Prior Approval Supplement and Pediatric Exclusivity Determination Request
Brand Name	IBRANCE ®
Generic Name	Palbociclib
Dosage Form and Strength	Capsules (125 mg, 100 mg, and 75 mg) Tablets (125 mg, 100 mg, and 75 mg)
Route of Administration	Oral
Approved Indications	• for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with: o an aromatase inhibitor as initial endocrine-based therapy; or o fulvestrant in patients with disease progression following endocrine therapy. • in combination with inavolisib and fulvestrant for the treatment of adult patients with endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or after completing adjuvant endocrine therapy. *Note: No new indication is proposed in the current supplement.*
Approved Dosages	125 mg taken orally once daily for 21 days followed by 7 days off treatment
Associated IND	135210
Pharmacometrics Reviewer	Junshan Qiu
Clinical Pharmacology Reviewer	Om Anand
Pharmacometrics Team Lead	Jingyu Yu
OCP Secondary Review	Lauren Price
OCP Final Signatory	Ruby Leong

1. Executive Summary

IBRANCE® (palbociclib) is an orally available, CDK4 and CDK6 inhibitor.

The Applicant submitted these supplemental NDAs (sNDAs) to fulfill the commitments as agreed in the final pediatric Written Request Amendment 3 dated 4 February 2025[1], regarding studies to investigate the potential use of palbociclib in the treatment of recurrent/refractory (r/r) pediatric solid tumors, including Ewing sarcoma (EWS).

The Applicant is not seeking an indication for palbociclib in pediatric patients with r/r EWS or any other solid tumor based on the lack of efficacy observed in the pediatric patient population across three clinical studies (A5481092, PBTC-042, and APEC1621I). The Applicant proposed updating the USPI with safety, efficacy, and pharmacokinetic (PK) information from the pediatric studies and is seeking a Pediatric Exclusivity Determination.

The submission includes clinical pharmacology data from the pediatric studies, including population pharmacokinetic (PopPK) modeling analysis across pediatric age groups. Additionally, bioequivalence data supporting the palbociclib oral solution relative to commercial capsules, along with food effect and gastric acid-modifying agent interaction studies for the oral solution formulation, were submitted.

The Applicant does not plan to seek marketing authorization for the age-appropriate oral solution formulation that was developed to support the pediatric studies, since no pediatric indication will be included in the USPI.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 207103/S-023 and NDA 212436/S-011. These supplements have met the components of the Written Request Amendment 3 and are approvable from a clinical pharmacology perspective. The proposed labeling changes with the FDA recommended modifications for Clinical Pharmacology-related sections are acceptable.

[1] DARRTS NDA-207103: COR-PEDEX-02 (Pediatric - Revised Written Request) 02/04/2025 LINK

2. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

2.1 Overview of the Regulatory Background

The Applicant submitted a Proposed Pediatric Study Request (PPSR)[2] for palbociclib on May 3, 2017, and a revised PPSR[3] on March 6, 2018, and requested the issuance of a Written Request for the evaluation of palbociclib in patients with r/r pediatric solid tumors, including EWS, to support the use of palbociclib in the pediatric population.

Following multiple correspondence regarding the PPSR, a Written Request for palbociclib was issued on July 3, 2018. Subsequently, the Written Request was amended three times between February 2021 and February 2025. The Applicant received a final Pediatric Written Request Amendment 3[4] (dated: 02/04/2025). Refer to the Clinical Review for additional information on the Pediatric Written Request development process and changes in each amendment.

The final Pediatric Written Request Amendment 3 consisted of three studies (see Table 1) that investigated the use of palbociclib in pediatric patients with r/r solid tumors, including EWS.

Table 1: Description of Each Study in Written Request

Study	Description
Study #1 (A5481092 (NCT03709680))	An open-label Phase 1/2 study to evaluate palbociclib in combination with irinotecan (IRN) and temozolomide (TMZ) and palbociclib in combination with topotecan (TOPO) and cyclophosphamide (CTX) in 98 pediatric patients, aged 2 to <17 years, with r/r solid tumors including neuroblastoma and EWS.
Study #3 (PBTC-042 (NCT02255461))	A Phase 1 study of palbociclib in 27 pediatric patients, aged 4 to <17 years, with Rb1-positive recurrent, progressive, or refractory primary CNS tumors.
Study #4 (APEC1621I (NCT03526250))	A single arm Phase 2 study of palbociclib in 15 pediatric patients, aged 9 to <17 years, with r/r solid tumors harboring activating alterations in cell cycle genes.

Note: There was no "Study #2" in the final Pediatric Written Request Amendment 3.

In addition to the three efficacy studies listed above, the Applicant conducted supporting clinical pharmacology studies to characterize the pediatric oral solution formulation:

Study A5481079: Combined bioequivalence and food effect study that evaluated:

- Bioequivalence study comparing palbociclib oral solution (25 mg/mL) versus

[2] IND-135210: COR-PEDEX-03 (Pediatric - Inadequate PPSR): 11/06/2017: LINK [Reference ID: 4177776]
[3] IND-135210: COR-PEDEX-01 (Pediatric - Written Request): 07/03/2018: LINK [Reference ID: 4286429]
[4] NDA-207103: COR-PEDEX-02 (Pediatric - Revised Written Request): 02/04/2025: LINK [Reference ID: 5524470]

commercial capsules under fed conditions.

- Food effect evaluating palbociclib oral solution under fed versus fasted conditions.

Study A5481041: Study evaluating the effect of concomitant administration of a gastric acid-modifying agent (rabeprazole) on the relative bioavailability of palbociclib oral solution.

The Applicant completed the studies and submitted supplemental NDAs (sNDA 207103 S-023 and sNDA 212436 S-011) to fulfill the Written Request commitments. Based on the lack of efficacy observed across all three clinical studies, the Applicant is not seeking an indication for palbociclib in pediatric patients; however, the Applicant updated the USPI with pediatric information and is requesting Pediatric Exclusivity Determination. The Applicant does not plan to seek marketing authorization for the age-appropriate oral solution formulation since no pediatric indication will be included in the USPI.

2.2 General Pharmacological and Pharmacokinetic Characteristics

The clinical pharmacology of palbociclib has previously been described in detail in the clinical pharmacology review of the original NDA 207103 submission. Refer to the original NDA Clinical Pharmacology Review[5] for a detailed description of the clinical pharmacology data.

Briefly, for the capsule formulation in adults, the median (min, max) time to maximal plasma concentration (Tmax) is 8 hours [6, 12] following oral administration. Palbociclib exhibits dose-proportional pharmacokinetics over the dose range of 25 mg to 225 mg for the capsule formulation. In patients with advanced cancer, the mean absolute bioavailability after a single oral 125 mg dose is 46%. The geometric mean (CV%) apparent oral clearance (CL/F) and apparent volume of distribution (Vz/F) at steady state are 63 L/h (29%) and 2,583 L (26%), respectively. The mean plasma elimination half-life is 29 hours (±5 hours). Steady state is achieved within 8 days following repeated once daily dosing, with a median (min, max) accumulation ratio of 2.4 [1.5, 4.2].

Food intake increased palbociclib exposure, for the capsule formulation, by 12-21% for AUC and 24-38% for Cmax depending on meal composition (high-fat/high-calorie: 21% AUC, 38% Cmax; low-fat/low-calorie: 12% AUC, 27% Cmax; moderate-fat: 13% AUC, 24% Cmax), and reduced inter-subject variability compared to fasted conditions, supporting the administration with food.
Palbociclib is extensively metabolized primarily via hepatic metabolism through CYP3A4 and SULT2A1, with renal elimination playing a minor role (6.9% of dose excreted unchanged in urine).

[5] DARRTS: REV-CLINPHARM-21 (Primary Review): NDA207103:01/15/2015 (Reference ID: 3686997) LINK

2.2 **Clinical Pharmacology Questions**

(a) **How do the exposure and PK parameters of palbociclib in pediatric patients compare to that of adult patients receiving the approved recommended starting dose of 125 mg QD**?

The Sponsor conducted a PopPK analysis based on data from Studies PBTC-042 and A5481092 to evaluate palbociclib PK in pediatric patients vs adults. The PopPK model included data from 114 pediatric patients aged 1 to <17 years and 25 patients aged >17 years who received who received palbociclib at dosages from 50 to 95 mg/m2 QD. The Sponsor utilized the final model to simulate palbociclib exposure after administration of 75 mg/m^2 QD (approximately the approved adult dosage of 125 mg QD using a typical BSA of 1.67 m^2 for adults). Based on the PopPK analysis, palbociclib dose-normalized exposure was similar across all pediatric age groups (≤6 years, 6 to <12 years, 12 to <17 years) and with adults (≥17 years). Table 2 summarizes the simulated palbociclib steady-state exposure in pediatric patients compared with adults, with exposures normalized to a dosage of 75 mg/m^2 QD palbociclib (*See Section 4 Appendix for details)*.

Table 2: Summary of Simulated Palbociclib Steady-State Exposure in Pediatric vs Adult Patients

Parameter; mean (CV%)	**<17 years (n=114)**	**≥17 years (n=25)**
$AUC_{0\text{-}24h}$ (ng*hr/mL)		
Mean (SD)	1,520 (496)	1,790 (595)
Median [Min, Max]	1,530 [373, 3,440]	1,690 [799, 3,270]
Cmax (ng/mL)		
Mean (SD)	90.1 (28.4)	97.0 (32.6)
Median [Min, Max]	92.8 [23.0, 172]	98.5 [38.8, 163]

Source: Section 4 Appendix Table 4.1

The analysis demonstrates that pediatric and adult patients receiving the same BSA-adjusted dosage of 75 mg/m² QD achieve similar systemic exposures. Body surface area-normalized PK parameters (CL/F and Vc/F) further support this similarity, demonstrating that the pharmacokinetics of palbociclib is similar in adults and pediatric patients.

In addition, palbociclib exposure after administration of 75 mg/m^2 QD was within the range observed in adults given the approved recommended dosage of 125 mg QD (~75 mg/m^2). Steady-state palbociclib exposures after administration of 125 mg QD in adult patients with advanced cancer are shown in Table 3.

Table 3: Summary of Palbociclib Steady-State Exposure After Administration of 125 mg QD Palbociclib in Adult Patients with Advanced Cancer

Study Number	Geometric mean (CV%)	
	AUC_{0-24h} (ng*hr/mL)	Cmax (ng/mL)
A5481001 (n=13)	1,633 (59%)	94.9 (48%)
A5481003 (n=12)	1,982 (29%)	116 (28%)

Source: Original NDA 207103 Clinical Pharmacology Review; Table 5

See the PopPK analysis summary (Section 4 Appendix Table 1) for detailed exposure metrics across pediatric age groups. These comparisons support the labeling statement that "palbociclib exposures in pediatric patients were within range of those observed in adults given a similar dose based on body surface area".

2.2.1 Do the components in the current submission fulfill the Written Request – Amendment 3 from a clinical pharmacology perspective?

Yes, the review team agrees that the components in the current submission meet the WR requirements from a clinical pharmacology perspective.

The Applicant provided PK data across required age groups, conducted appropriate popPK modeling and exposure-response (E-R) analyses, and demonstrated adequate characterization of palbociclib PK in the pediatric population. Written Request Amendment 3 components pertinent to Clinical Pharmacology are summarized below.

i. PK studies and sample sizes

Study 1 (A5481092) Enrollment Summary:

Study Phase	Treatment Combination	Palbociclib Dose[6]	WR Requirement	Actual Enrollment
Phase 1 Dose Escalation	Palbociclib+IRN+TMZ	55, 75, 95 mg/m²	A minimum of 6 patients to a maximum of 24 DLT evaluable patients with recurrent or refractory solid tumors	16 DLT-evaluable patients with r/r solid tumors
Phase 1 Dose Determination	Palbociclib+TOPO+CTX	75 mg/m²	A minimum of 6 to a maximum of 12 DLT evaluable patients with recurrent or refractory solid tumors	6 DLT-evaluable patients with r/r solid tumors
Phase 1 Dose Expansion	Each palbociclib combination	75 mg/m²	A minimum of 12 patients (for each palbociclib combination) with recurrent or refractory solid tumors	Palbociclib+IRN+TMZ: 17 patients with r/r solid tumors Palbociclib+TOPO+CTX: 20 patients r/r solid tumors
Tumor-Specific Cohort	Palbociclib+TOPO+CTX	75 mg/m²	Maximum of 21 patients per cohort if anti-tumor activity is observed	7 patients with neuroblastoma

[6] Palbociclib dose levels. The combination agents (IRN, TMZ, TOPO, CTX) were administered at fixed doses throughout the studies.

Phase 2 Randomized	Total Phase 2	75 mg/m²	Approximately 75 patients (~50 patients in the palbociclib in combination with IRN and TMZ arm and ~25 patients in the IRN and TMZ arm). At least 60% of patients enrolled in each arm will be under the age of 18. An analysis for futility will be conducted; fewer patients may be enrolled if the futility criteria are met.	63 patients (42 palbociclib+IRN+TMZ arm, 21 IRN+TMZ arm, 85.7% <18 years old; stopped due to futility)

Study 3 (PBTC-042) - CNS Tumors: Palbociclib monotherapy

Component	Palbociclib Dose	WR Requirement	Actual Enrollment
Total Enrollment	50, 75, 95 mg/m²	A maximum of 55 patients with Rb1-positive recurrent, progressive, or refractory primary CNS tumors ≥4 years and ≤21 years of age	34 patients with Rb1-positive recurrent, progressive, or refractory primary CNS tumors ≥4 years and ≤21 years of age
Stratum 1 (less-heavily pretreated participants)	50, 75, 95 mg/m²	Part of maximum 55 patients	21 patients (less-heavily pretreated), Median (min, max) age: 11 years (4, 21)
Stratum 2 (heavily pretreated participants)	50, 75, 95 mg/m²	Part of maximum 55 patients	13 patients (heavily pretreated), Median (min, max) age: 12 years (6, 21)
Dose Distribution			
	50 mg/m²	*Not specified*	7 patients
	75 mg/m²	*Not specified*	21 patients
	95 mg/m²	*Not specified*	6 patients

Study 4 (APEC1621I) - Biomarker-Selected Tumors: Palbociclib monotherapy

Component	Palbociclib Dose	WR Requirement	Actual Enrollment
Total Enrollment	75 mg/m²	A maximum of 49 patients with advanced solid tumors, NHL or histiocytic disorders that harbor activating genetic alterations in cell cycle genes ≥12 months to ≤21 years	20 patients with advanced solid tumors, NHL or histiocytic disorders that harbor activating genetic alterations in cell cycle genes ≥12 months to ≤21 years
Age Distribution	75 mg/m²	≥12 months to ≤21 years	1-6 years (0), 7-11 years (5), 12-16 years (10), 17-21 years (5)

Age-Stratified PK Analysis:

Study 1 Age Distribution

Age Group	WR Requirement	Actual Enrollment	
		Palbociclib+IRN+TMZ	Palbociclib+TOPO+CTX
≤6 years	Minimum 6 patients	13 patients	8 patients
>6-<12 years	Minimum 6 patients	12 patients	11 patients
≥12-<18 years	Minimum 6 patients	32 patients	8 patients
≥18 years	*Not specified*	11 patients	4 patients
Total	Minimum 18 per combination	68 patients with PK data	31 patients with PK data

Studies 3 and 4 Age Distribution

Study	WR Requirement	Actual Enrollment
Study 3 (PBTC-042)	A maximum of 55 patients with Rb1-positive recurrent, progressive, or refractory primary CNS tumors ≥4 years and ≤21 years of age	34 patients total Median age: 12 years Stratum 1: 21 patients (median 11 years) Stratum 2: 13 patients (median 12 years)
Study 4 (APEC1621I)	A maximum of 49 patients with advanced solid tumors, NHL or histiocytic disorders that harbor activating genetic alterations in cell cycle genes ≥12 months to ≤21 years	20 patients total 1-6 years: 0 patients 7-11 years: 5 patients 12-16 years: 10 patients 17-21 years: 5 patients

Review Team Comment:
Study 1: Each age group exceeded the minimum requirement of 6 patients per treatment combination (palbociclib+IRN+TMZ and palbociclib+TOPO+CTX) with reportable PK parameters. Age-stratified enrollment met WR requirements.
Study 3:PK sampling was adequate across all dose levels (50, 75, 95 mg/m²) for single-agent palbociclib characterization in patients with CNS tumors.
Study 4: Single-dose level enrollment provided adequate data for biomarker-selected tumor population.
All studies met their respective WR requirements for pediatric PK characterization.

ii. Population PK Modeling

PopPK Analysis (PMAR-EQDD-A548d-sNDA-3231):

- Pooled data approach: Integrated Studies 1 and 3 as required by WR
- Model development: Population PK model characterizing palbociclib in pediatric participants
- Covariate analysis: Investigation of age and body size effects on CL/F and Vd/F
- Individual parameters: Post-hoc PK parameters (CL/F, Vd/F) reported by age groups

Exposure Comparisons:

- Palbociclib exposure across age groups was similar based on comparison of mean dose normalized AUCtau, Cmax, and Ctrough
- Dose-normalized PK parameters showed consistency across pediatric age groups

Review Team Comment: *The WR specified minimum enrollment by age groups, and the analysis provided individual exposure metrics provided for ≤6, 6-<12, and 12-<18 year age groups. This fulfills the WR mandate for pooled popPK analysis using Studies 1 and 3 data. Dose-normalized PK parameters were evaluated per the age groups listed in the WR.*

iii. Exposure-Response Relationships

Population PK/PD Analysis (PMAR-EQDD-A548d-sNDA-3232):

- Safety E-R modeling: Exposure-response analysis for neutropenia
- Model development: popPK/PD model describing absolute neutrophil count (ANC) dynamics
- Pediatric-adult comparison: comparable ANC dynamics across age groups and to adults
- Investigation of potential covariates that may impact the palbociclib exposure-response for neutropenia in pediatric participants.
- Model simulations supported similar tolerability observed between pediatrics and adults at equivalent concentrations.
- Efficacy E-R Analysis: Efficacy E-R analysis was not conducted due to heterogeneity of tumor types in the Phase 1 portion of Study 1 and Study 3, and the interim analysis outcome (futility) of the Phase 2 portion of Study 1.

Review Team Comment: *Exposure-response analysis for the clinically relevant safety endpoint of neutropenia as specified in the WR was conducted. The E-R analysis component meets the WR requirements. The decision not to conduct efficacy E-R analysis is deemed appropriate given the study outcomes (futility) and patient population heterogeneity.*

iv. PK Data Package Supporting Pediatric Dosing

Dose-Proportionality Assessment:

- Documented linearity: Steady-state palbociclib exposure increased dose-proportionally from 55 to 95 mg/m².
- Multiple dose levels evaluated: 55, 75, and 95 mg/m² across combination therapies.

Steady-State Characterization:

- Achievement confirmed: C1D5 to be approximately at steady-state based on trough concentration comparisons
- Consistent across visits: Comparable Ctrough between C1D5, C1D14, C2D5, and C2D14

Pediatric-Adult Exposure Comparison:

- Equivalent exposures demonstrated: Palbociclib exposure on C1D5 in pediatric patients who received 75 mg/m² was within the range of exposure observed in adult patients who received 125 mg
- Clinical relevance: Supports comparison of palbociclib exposure between pediatric patients and adults

Drug Interaction Assessment:

- Combination therapy PK: Complete characterization of palbociclib, TMZ, IRN/SN-38, TOPO, and CTX

- No clinically significant interactions: All combination agents showed expected PK profiles.

v. Bioanalytical Method

- Previously validated bioanalytical method for palbociclib quantification was used to analyze pediatric patient plasma levels using LC-MS/MS.
- The method demonstrated accuracy (inter-run accuracy: -6.95% to 5.84% RE), precision (inter-run precision: ≤7.0% CV), and linearity (1 to 250 ng/mL with LLOQ of 1 ng/mL) across both pediatric studies (PBTC-042 and A5481092).
- Incurred sample reanalysis demonstrated method reproducibility.

Review Team Comment: *The PK data package fulfills WR requirements by demonstrating appropriate PK characterization across dose levels, confirming steady-state achievement, and establishing pediatric-adult exposure comparability. This supports evidence-based pediatric dosing recommendations as specified in the WR.*
Bioanalytical method for palbociclib, including study-specific performance verification, is acceptable in characterizing the concentrations of palbociclib in pediatric patients.
The submission meets all WR requirements from a clinical pharmacology perspective and incorporates relevant findings into product labeling.

2.2.2 Are other changes to the labeling warranted based on the pediatric clinical pharmacology data in the sNDAs?

No, no other changes to the labeling are warranted beyond the pediatric PopPK information for Section 8.4.

The submission includes additional clinical pharmacology data such as bioequivalence studies of the palbociclib oral solution to commercial capsules, food effect studies, and gastric acid-modifying agent interaction studies for the oral solution formulation. However, these data do not warrant inclusion in the labeling since the Applicant does not plan to seek marketing authorization for the age-appropriate oral solution formulation that was developed to support the pediatric studies, given that no pediatric indication will be included in the USPI.

3 LABELING CHANGES

The proposed key labeling changes, and the recommended Clinical Pharmacology changes are summarized below.

Section 8.4: Pediatric Use:

- Proposed: (b) (4) [redacted]
- Recommended/Revised: Palbociclib exposures in pediatric patients who received IBRANCE as a single agent or in combination were within range of those observed in adults given a similar dose based on body surface area.

(b) (4)

Reviewer comments:

- *Added pediatric exposures information to Section 8.4 based on popPK analysis (see details in Appendix 4).*
- (b) (4)

[7] FDA Guidance for Industry - Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling March 2019 LINK

4. APPENDIX

4.1 Pharmacometrics Memo

Background and Overview: Palbociclib (IBRANCE®, PD-0332991) is a CDK 4/6 inhibitor, which is approved for the treatment of adult patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy or in combination with fulvestrant in patients with disease progression following endocrine therapy. The recommended starting dosage of palbociclib for adult patients is 125 mg taken orally QD for 21 consecutive days followed by 7 days off treatment in each cycle of 28 days. In the initial approval, the geometric mean area under the plasma concentration-time curve (AUC) from time 0 to 24 hours ($AUC_{[0-24]}$) and Cmax for palbociclib at steady state in patients with advanced breast cancer were 1982 ng*hr/mL and 116 ng/mL, respectively. The adult exposure metrics are comparable across the applications.

Data and Method: The PopPK model for palbociclib in pediatric participants in Study PBTC-042 and Study A5481092 was a 2-compartment model with first-order absorption. The final PopPK model provides post-hoc estimates that were used to generate individual concentration-time profiles to derive exposure values with each subject administered 75 mg/m^2 times baseline BSA.

Conclusion: Ten patients aged 17 years were regrouped as adults and the summary of statistics on PK, exposure and key demographic parameters are shown in Table A4.1. The results support the label statement in section 8.4 "*Palbociclib exposures in these pediatric patients who received IBRANCE as a single agent or in combination was within range of those observed in adults given a similar dose based on body surface area*".

Table A4.1. Summary of Exposure Metrics on C1D14 and PK Parameters Stratified by Age Group 3

	A) Age < 17 (N=114)	B) Age >= 17 (N=25)	Total (N=139)
C1D14 AUC24 (ng*hr/mL)			
Mean (SD)	1520 (496)	1790 (595)	1570 (523)
Median [Min, Max]	1530 [373, 3440]	1690 [799, 3270]	1550 [373, 3440]
C1D14 Cmax (ng/mL)			
Mean (SD)	90.1 (28.4)	97.0 (32.6)	91.4 (29.2)
Median [Min, Max]	92.8 [23.0, 172]	98.5 [38.8, 163]	93.0 [23.0, 172]
BBSA normalized CL/F (L/hr/m^2)			
Mean (SD)	23.1 (13.0)	15.8 (5.27)	21.8 (12.3)
Median [Min, Max]	19.7 [7.04, 86.4]	14.1 [8.22, 32.2]	18.9 [7.04, 86.4]
BBSA normalized Vc/F (L/m^2)			

and PK Parameters Stratified by Age Group 3

	A) Age < 17 (N=114)	B) Age >= 17 (N=25)	Total (N=139)
Mean (SD)	201 (173)	209 (181)	202 (174)
Median [Min, Max]	142 [12.1, 847]	125 [54.3, 682]	142 [12.1, 847]
Age (year)			
Mean (SD)	10.3 (4.50)	18.3 (1.38)	11.8 (5.14)
Median [Min, Max]	11.0 [1.00, 16.0]	18.0 [17.0, 21.0]	12.0 [1.00, 21.0]
Baseline BSA (m^2)			
Mean (SD)	1.29 (0.440)	1.85 (0.356)	1.39 (0.478)
Median [Min, Max]	1.27 [0.500, 2.36]	1.77 [1.45, 2.97]	1.44 [0.500, 2.97]
Palbociclib simulated dose (mg)			
Mean (SD)	96.5 (33.0)	138 (23.9)	104 (35.3)
Median [Min, Max]	94.9 [37.5, 177]	133 [109, 200]	108 [37.5, 200]

Source: Reviewer's analyses
Note: Simulated dose represents individual patient dose calculated as 75 mg/m² × baseline BSA

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