



IND 135210
NDA 207103

WRITTEN REQUEST – AMENDMENT 3

Pfizer, Inc.
Attention: Lisa Rysso-DeMaggio, BS, RAC
Director, Pfizer Global Regulatory Strategy
10646 Science Center Dr.
San Diego, CA 92121

Dear Ms. Rysso-DeMaggio:

Please refer to your correspondences dated October 7, 2024, January 17, 2025, and February 4, 2025, requesting changes to FDA's July 3, 2018, Written Request for pediatric studies for Ibrance (palbociclib).

We have reviewed your proposed changes and are amending the Written Request to incorporate the following changes:

- edits for clarity and brevity,
- minor revisions related to categorization of race and ethnicity,
- updates based on Study 1 completion following conduct of a planned interim analysis, and
- clarifications related to the submission of study reports.

All other terms stated in our Written Request issued on July 3, 2018, and as amended on February 2, 2021, and September 23, 2021, remain the same.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated July 3, 2018, as amended by this letter and by previous amendment(s) dated February 2, 2021 and September 23, 2021, must be submitted to the Agency on or before December 5, 2025, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **“SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED”** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.¹

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **“PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES”** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, contact Maritsa Stephenson, Regulatory Project Manager, at Maritsa.Stephenson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Martha Donoghue, M.D.
Acting Associate Director, Pediatric Oncology
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Copy of the Written Request as Amended, with Changes Marked
- Complete Copy of Written Request as Amended

¹ <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm>



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WRITTEN REQUEST – AMENDMENT #3

Pfizer, Inc.
Attention: Lisa Rysso-DeMaggio, BS, RAC
Director, Pfizer Global Regulatory Strategy
10646 Science Center Dr.
San Diego, CA 92121

Dear Ms. Rysso-DeMaggio:

Please refer to your correspondence dated October 7, 2024, January 25, 2025, and February 4, 2025, requesting changes to FDA's July 3, 2018, Written Request for pediatric studies for Ibrance (palbociclib).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on July 3, 2018, and as amended on February 2, 2021, and September 23, 2021, remain the same. (Text added is underlined and text deleted is strikethrough).

BACKGROUND:

These studies will investigate the potential use of palbociclib in the treatment of recurrent/refractory pediatric solid tumors, including Ewing sarcoma (EWS).

Palbociclib (PD-0332991) is a highly selective, reversible, small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6, administered orally. Cyclin D1 and CDK4/6 are downstream of multiple signaling pathways which lead to cellular proliferation. Through inhibition of CDK4/6, palbociclib reduces cellular proliferation by blocking progression of the cell from G1 into S phase of the cell cycle. There is interest in CDK 4/6 inhibitors given the mechanism of action and their effect on cell proliferation which is potentially applicable to many types of adult and pediatric cancers. Palbociclib (IBRANCE®) is currently indicated for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer (MBC) in combination with an aromatase inhibitor as initial endocrine-based therapy ~~in postmenopausal women or in men~~, or fulvestrant in patients with disease progression following endocrine therapy. Since breast cancer does not occur in children or adolescents, the benefit of palbociclib demonstrated in HER2-, HR+ MBC cannot be extrapolated to alternate tumor types in the pediatric setting at this time. However, dysregulated cyclin D-CDK4/6 activity has been implicated as a regulator of cell cycle progression in some pediatric cancers, such as neuroblastoma, rhabdoid tumor, medulloblastoma, EWS and RMS.

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According to the American Cancer Society, EWS accounts for 1% of all childhood tumors, with an estimated 225 children and teens diagnosed each year in North America (American Cancer Society, 2017a). Recurrent EWS develops in 30%-60% of children, depending on treatment regimen and study population. Recurrent/metastatic EWS has a poor prognosis, with less than 20% 5-year overall (Stahl et al, 2011). There is no standard second-line treatment. The choice of regimen depends on the type of relapse (local versus metastatic disease), time to relapse, the patient's general condition, and previous first-line treatment.

Studies of palbociclib in neonates are not required because children < 2 years of age are excluded from the studies in this Written Request since relapsed/refractory EWS is unlikely to occur in infants and young children. As well, children < 2 years of age are excluded from the clinical development plan of palbociclib due to the possible risk of them developing diabetes based on nonclinical toxicity data.

To obtain needed pediatric information on palbociclib, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

Additional Background Information Influencing Proposed Studies and Endpoints

The original pediatric Written Request included Study 2, which was designed to add a randomized component to the rEECur study to assess the antitumor activity of palbociclib in combination with a standard backbone chemotherapy regimen after sufficient information was obtained in Study 1 to support the safety and antitumor activity of palbociclib in Study 1. The rEECur study, conducted by the University of Birmingham (Sponsor) and the EuroEwing Consortium (EEC), is an ongoing multi-stage, multi-arm, international, randomized controlled trial in patients with recurrent and primary refractory Ewing sarcoma evaluating 4 chemotherapy regimens [gemcitabine (GEM)+docetaxel (DOX), irinotecan (IRN)+temozolomide (TMZ), topotecan (TOPO)+cyclophosphamide (CTX), high-dose ifosfamide (IFOS)], with the goal of identifying two chemotherapy arms to continue to a Phase 2 comparison.

In March 2020, results from the second interim assessment of the rEECur Study suggested that the clinical activity of the IRN+TMZ and TOPO+CTX combinations or single-agent IFOS were comparable; the observed overall response rate (ORR) was 20% in the IRN+TMZ arm versus 23% in the IFOS and TOPO+CTX combined arms and the median progression-free survival (PFS) was 4.7 months for IRN+TMZ versus 5.3 months for IFOS and TOPO+CTX combined (McCabe et al, 2020). The EEC also reported that the response rate in this clinical trial at the second interim assessment timepoint did not correlate well with the PFS and OS outcomes in patients with recurrent and/or primary refractory EWS (Wheatley et al, 2020). Considering the lack of a clear correlation between ORR and survival parameters and the minimal rate of second malignancies in the studied patient population within

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the rEECur trial to date, the EEC changed the primary endpoint of the Phase 2 portion of rEECur to EFS. The IRN+TMZ chemotherapy arm was subsequently discontinued from the rEECur study and in February 2021, the Written Request was amended to change the backbone in Study 2 to TOPO+CTX. Amendment #1 incorporated additional changes to Study 2 to specify collection of sparse PK samples for palbociclib, topotecan, and cyclophosphamide in all pediatric patients (ages > 2 to < 18 years). Amendment #1 also revised Study 1 to include TOPO+CTX as an additional backbone for combination dose escalation with palbociclib based on the results from Study 2, to specify a minimum number of patients to be enrolled in each age group, and state that tumor specific cohorts may be opened as warranted based on signals of anti-tumor activity observed in the dose finding and dose expansion parts of Study 1.

In March 2021, the EEC temporarily suspended recruitment to the TOPO+CTX arm due to observed differences, unrelated to safety, between the outcomes of patients randomized to the TOPO+CTX and high dose IFOS arms. Due to challenges and delays in introducing a palbociclib/backbone chemotherapy combination into the rEECur study, the Written Request was amended again in September 2021 to remove Study 2 and add a randomized component with a primary EFS efficacy endpoint to Study 1 comparing palbociclib in combination with IRN+TMZ to IRN+TMZ alone in lieu of conducting a separate randomized trial for feasibility (Amendment 2). The revision to Study 1 was designed in conjunction with advice and support from the Children's Oncology Group (COG). COG agreed that IRN+TMZ is standard of care for this population in the United States and may have less toxicity than TOPO+CTX or high-dose IFOS.

The WR was most recently amended in February 2025 to include edits for clarity and brevity, minor revisions related to categorization of race and ethnicity, updates based on Study 1 completion following conduct of a planned interim analysis, and clarifications related to the submission of study reports (Amendment #3). Results of a planned analysis of Study 1 Stage 1 tumor specific cohort indicated that palbociclib in combination with TOPO and CTX is ineffective for patients with recurrent or refractory neuroblastoma (NB); therefore, additional enrollment of the NB tumor specific will not occur and Study 1 tumor specific cohort will not proceed to Stage 2.

- *Nonclinical study(ies):*

Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*

Study 1 (Study A5481092): A Phase 1/2 open-label study to evaluate palbociclib in combination with TMZ and IRN and palbociclib in combination with TOPO and CTX in children, adolescent, and young adult patients with relapsed or refractory solid

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tumors. The non-randomized Phase 1 portion of the study will evaluate the safety, pharmacokinetics (PK) and antitumor activity of palbociclib in combination with TMZ and IRN and palbociclib in combination with TOPO and CTX in patients with relapsed or refractory solid tumors. The randomized Phase 2 portion of the study will further evaluate the efficacy, safety, and PK of palbociclib in combination with IRN and TMZ in children, adolescents, and young adults with recurrent or refractory EWS.

In the Phase 1 portion of Study 1, the dose-escalation/determination part will include pediatric patients with recurrent or refractory solid tumors. The dose expansion portion for each combination will first enroll and treat a minimum of 12 patients with any recurrent or refractory solid tumor type to confirm the palbociclib recommended Phase 2 dose (RP2D) for each combination. If 2 or more patients from the dose escalation/determination parts and/or dose expansion cohorts from either combination show an objective response within a specific tumor type (such as neuroblastoma, RMS, rhabdoid tumors, or medulloblastoma), a tumor-specific cohort will be opened to further evaluate anti-tumor activity of the respective combination within the specific cancer subtype.

If tumor-specific cohorts with palbociclib in combination with either TMZ and IRN or TOPO and CTX are opened, then a modified Simon's 2-stage optimal design will be followed with the decision rules as shown below. Under the null hypothesis of a true ORR that does not exceed 33%, the 2-stage optimal design will control 1-sided type I error to be approximately 0.10. If the true ORR is at least 58%, type II error will be no more than 0.20 (i.e., at least 80% power) ([Table 1](#)).

Table 1. Modified Simon's 2-Stage Optimal Design Decision Rules for Other Tumor Specific Cohorts

	Cumulative Number of Responses ^a	Decision
Stage 1: Enroll a total of 7 patients^b	2	Terminate enrollment-agent ineffective
	3 – 5	Inconclusive-proceed to Stage 2
	6 ^c	Terminate enrollment-agent effective
Stage 2: Enroll 14 additional patients (N=21 total)	9 or less	Agent ineffective
	10 or more	Agent effective

Table 1. Modified Simon's 2-Stage Optimal Design Decision Rules for Other Tumor Specific Cohorts

	Cumulative Number of Responses ^a	Decision
a.	Assumption based on an objective response rate of 33% for IRN/TMZ or TOPO/CTX and 58% for palbociclib/IRN/TMZ or palbociclib/TOPO/CTX, respectively	
b.	Evaluated patients will include the 2 objective responses observed and any other patients with the same tumor type during the dose escalation and dose determination part and dose expansion cohort of the study.	
c.	Lower bound of the Wilson's 2-sided 80% CI is greater than 62%	

The open-label, randomized Phase 2 portion of Study 1 will evaluate the efficacy, safety, PK and pharmacodynamic (PD) activity of palbociclib in combination with IRN and TMZ versus IRN and TMZ alone in children, adolescent, and young adult patients with recurrent or refractory EWS. Of note, although patients with EWS can enroll into the dose escalation part and the dose expansion cohort of the study for palbociclib in combination with IRN and TMZ, a tumor specific cohort for EWS will not be opened in Study 1 for this combination since the randomized Phase 2 portion will enroll patients with EWS to evaluate efficacy of palbociclib in combination with IRN and TMZ.

The Phase 2 portion of Study 1 will randomize ~~up to a total of~~ approximately 75 eligible patients (age ≥2 and <21 years) with recurrent or refractory EWS, using 2:1 randomization, stratified using block randomization by type and time of current disease recurrence (primary refractory or 1st recurrence < 2 years versus 1st recurrence ≥ 2 years or 2nd or greater recurrence). It is expected approximately 75% of the patients will be pediatric patients (age ≥2 and <18 years). A total of approximately 50 EFS events are required in the two treatment arms of the study to have at least 80% power to detect a hazard ratio of 0.58 in favor of palbociclib in combination with IRN and TMZ arm using a 1-sided log-rank test at a significance level of 0.20. The study is considered hypothesis generating only.

~~A final Clinical Study Report (CSR) will be generated for Study 1 and will contain data from the Phase 1 dose finding and dose expansion parts for each combination in solid tumors and, if opened, any tumor specific cohorts, and the randomized Phase 2 portion in refractory or recurrent EWS for palbociclib in combination with IRN+TMZ versus IRN+TMZ alone to isolate the palbociclib effect.~~

~~The potential duration of the tumor specific cohorts, especially in these rare pediatric settings, may take an extended time to enroll and complete. If accrual to the disease specific cohorts of Study 1 is less than anticipated, sponsor may request an amendment to the Written Request.~~

Study 3: An open-label, Phase 1, dose escalation study to evaluate the safety and pharmacokinetics of palbociclib in pediatric patients with retinoblastoma protein 1 (Rb1)- positive recurrent, progressive, or refractory central nervous system (CNS) tumors (Study PBTC-042)

Study 4: An ~~ongoing~~, open-label, Phase 2 trial to evaluate single-agent palbociclib in pediatric patients with tumors harboring activating alterations in cell cycle genes (Study APEC1621I). ~~FDA recognizes that Study 4 (APEC1621I) may take a long time to accrue thereby delaying study completion and data submission. Should the results of the APEC1621I study become available prior to or at the completion for submission as described above of Studies 1 and 3, Pfizer will engage with the Sponsor of the APEC1621I study to request study results such as summary tables and listings to enable an abbreviated study report to be prepared and submitted at the time of submission for Studies 1 and 3. The Written Request may be amended upon request from Pfizer to either remove the Study 4 Written Request obligation or delay data submission in the event that results from Study 4 are not available for submission when Studies 1 and 3 are completed for submission.~~

Efficacy in pediatric patients ages ≥ 2 to < 18 years with recurrent or refractory EWS in the Phase 2 portion of **Study 1** will be supported by data in young adult patients (ages ≥ 18 to < 21 in **Study 1**), given the rarity of EWS in young pediatric patients and the fact that EWS occurs throughout adolescence and young adulthood. Most diagnoses of EWS occur in patients > 10 years of age. A minimum of ~~65~~50% of patients per arm enrolled in Study 1 Phase 2 must be < 18 years of age.

The confirmation of the recommended phase 2 dose (RP2D) from the Phase 1 portion of **Study 1** must be completed before initiating the open-label, randomized Phase 2 portion of **Study 1**.

- *Objective of each study:*

Study 1

Phase 1

Dose Escalation Part:

- To estimate MTD for the combination of palbociclib+TMZ+IRN in children, adolescents and young adults with recurrent or refractory solid tumors
- To characterize the safety profile of palbociclib combined with TMZ and IRN
- To describe the PK of palbociclib, TMZ, and IRN in children, adolescents and young adults when given in combination
- To evaluate the preliminary anti-tumor activity of palbociclib combined with TMZ and IRN

Dose Determination Part:

- To determine the potential RP2D for palbociclib in combination with TOPO and CTX in children, adolescents, and young adults with recurrent or refractory solid tumors.

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- To characterize the safety profile of palbociclib combined with TOPO and CTX.
- To describe the PK of palbociclib, TOPO, and CTX in children, adolescents, and young adults with recurrent or refractory solid tumors when given in combination
- To evaluate the preliminary anti-tumor activity of palbociclib combined with TOPO and CTX.

Dose Expansion Parts and Tumor-Specific Cohorts:

- To evaluate the safety and confirm the RP2D for the combination of palbociclib+TMZ+IRN and the combination of palbociclib+TOPO+CTX in children, adolescents and young adults with recurrent or refractory solid tumors, which may include RMS, EWS, and other disease-specific solid tumors.
- To evaluate the preliminary anti-tumor activity of palbociclib combined with TMZ and IRN and palbociclib combined with TOPO and CTX in children, adolescents and young adults with recurrent or refractory solid tumors, including disease-specific solid tumors.
- To describe the PK of palbociclib, TMZ and IRN and of palbociclib, TOPO and CTX in children, adolescents and young adults with recurrent or refractory solid tumors when given in combination.

Phase 2

- To compare the efficacy of palbociclib plus TMZ and IRN versus TMZ and IRN alone in the treatment of patients with recurrent or refractory EWS
- To characterize the toxicity, and safety of the combination of TMZ and IRN plus or minus palbociclib
- To describe the PK of palbociclib, TMZ, and IRN in patients with recurrent or refractory EWS when given in combination
- To assess the impact of the combination of palbociclib with TMZ and IRN treatment on the quality of life (QoL) of patients with recurrent or refractory EWS.

Study 3

- To determine the MTD/RP2D and describe toxicities related to palbociclib in children with Rb1-positive recurrent, progressive or refractory primary CNS tumors
- To determine plasma PK of palbociclib in children with Rb1-positive recurrent, progressive or refractory primary CNS tumors
- To record preliminary evidence of efficacy of palbociclib in children with recurrent CNS tumors

Study 4

- To determine the objective response rate (ORR) in pediatric patients treated with palbociclib with advanced solid tumors (including CNS tumors), non-Hodgkin lymphomas or histiocytic disorders that harbor activating genetic alterations in cell cycle genes
- To estimate progression free survival (PFS) in pediatric patients treated with palbociclib with advanced solid tumors (including CNS tumors), non-Hodgkin

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lymphomas or histiocytic disorders that harbor activating genetic alterations in cell cycle genes

- To obtain information about the tolerability of palbociclib in pediatric patients with relapsed/refractory cancer
- *Patients to be Studied:*

Study 1

Age ≥ 2 years and < 21 years at the time of study entry

Phase 1:

Dose Escalation Part (palbociclib in combination with IRN and TMZ): A minimum of 6 patients to a maximum of 24 DLT evaluable patients with recurrent or refractory solid tumors

Dose Determination Part (palbociclib in combination with TOPO and CTX): A minimum of 6 to a maximum of 12 DLT evaluable patients with recurrent or refractory solid tumors

Dose Expansion Parts: A minimum of 12 patients (for each palbociclib combination) with recurrent or refractory solid tumors with the possibility of opening additional tumor-specific cohorts (maximum of 21 patients per cohort) if anti-tumor activity is observed.

Phase 2:

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.

Study 3

A maximum of 55 patients with Rb1-positive recurrent, progressive, or refractory primary CNS tumors ≥ 4 years and ≤ 21 years of age.

Study 4

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.

Pooled Pharmacokinetic Analysis

Adequate pharmacokinetic (PK) samples of palbociclib will be collected in **Studies 1** and **3** in order to allow for determination of palbociclib PK parameters by non-compartmental analyses. PK sample collections of palbociclib will be included in the Phase 2 portion of **Study 1**, which will contribute to a pooled POP-PK analysis using pooled data from **Studies 1** and **3** to determine population PK parameters, such as the apparent clearance (CL/F) and volume of distribution (Vd/F) of palbociclib in

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pediatric patients. As the data allow, exposure-response relationships for safety and efficacy endpoints of interest may also be explored.

While the Sponsor should attempt to enroll 6 patients with each triplet combination, given the rarity of pediatric cancer patients in specified age ranges, a minimum of 6 patients treated with the combination of either palbociclib+TMZ+IRN or palbociclib+TOPO+CTX in **Study 1** will be enrolled in each of the following age groups: ≤ 6 years old, >6 years but <12 years, and ≥ 12 years old but <18 years to provide for a PK analysis by stratified age group. The PK sample collection plan for the patients contributing to these minimums of 6 patients per the 3 stratified age groups should be sufficient to allow for determination of palbociclib PK parameters by non-compartmental analyses.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

Study 1

Phase 1:

Dose Escalation/Dose Determination Parts:

- The primary endpoint will be first-cycle dose-limiting toxicities (DLTs).

Dose Expansion Parts and Tumor-Specific Cohorts:

- The primary endpoints are:
 - Adverse Events as characterized by type, frequency, severity, as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03), laboratory test data, electrocardiogram parameters, and vital signs
 - Objective tumor response (OR) as assessed using Response Evaluation Criteria in Solid Tumor (RECIST version 1.1) or modified Revised Assessment in Neuro Oncology (RANO) for CNS malignancies or International Neuroblastoma Response Criteria (INRC) criteria for neuroblastoma.
- Secondary endpoints will include:
 - Duration of Response (DOR), PFS, and Overall Survival (OS).
 - PK parameters of palbociclib, TMZ, IRN, TOPO, and CTX: multiple dose $C_{ss,max}$, T_{max} , $AUC_{ss,tau}$, $C_{ss,trough}$, and CL/F, as data permit.

Phase 2:

- The primary endpoint is event-free survival (EFS) based on investigator assessment.

- The secondary endpoints are:
 - Adverse events as graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.03 (all SAEs and non-serious AEs Grade ≥ 3 and other select non-serious AEs as defined by the protocol).
 - PK parameters of palbociclib, TMZ, and IRN when used in combination, as data permit
 - Objective response (OR) as assessed by investigator using RECIST version 1.1.
 - PET-CT response after Cycle 4 compared to OR on MRI/CT
 - PFS based on investigator assessment
 - OS
 - QoL at baseline and after 2 and 4 cycles using age-appropriate tools
 - Days of hospitalization

Study 3

- The primary endpoint is DLTs during the first course of treatment.
- The key secondary endpoints are:
 - Adverse Events as graded by NCI CTCAE version 4.03,
 - ORR,
 - Individual PK parameters of palbociclib

Study 4

- The primary endpoint is ORR as assessed by RECIST v1.1.
- The key secondary endpoints are:
 - PFS estimated using the Kaplan-Meier method, and
 - incidence of adverse events assessed by the current version of the NCI CTCAE

- *Known drug safety concerns and monitoring:*

Male reproduction: Effects on male reproductive organs (testis, epididymis, prostate, seminal vesicle) were observed in rats and dogs. The incidence and severity of testicular and epididymal findings were dose-related (minimal to severe) and often correlated with decreases in testicular and epididymal weights. Testicular degeneration produced by palbociclib was partially reversible after 12 weeks of dose-free period and is consistent with CDK inhibition and alteration of cell cycle kinetics, given the rapid and continuous cycling of germ cells. In Study 1, sexual development Reproductive effects will be monitored by study sites per their respective local standards protocol. Of note, patients enrolled into this study would have had previously received gonadotoxic therapy and will be difficult to isolate the effect of palbociclib versus prior therapies.

Bone: Effects on bone observed in male rats consisted of a mild to moderate decrease in trabeculae of the femur, characterized by decreased thickness of the

physis, decreased or segmental loss of primary and secondary spongiosa, and/or decreased trabeculae within the metaphysis. No recovery was observed in the femur where mild to marked decreased bone formation was observed. There were no palbociclib-related bone effects in female rats at higher doses and exposures or in dogs at any dose.

~~As part of the exploratory objectives in~~ The protocol for Study 1 will include provisions for monitoring, the effects of treatment with palbociclib on parameters of bone metabolism, ~~growth, and pubertal development~~ will be monitored, including linear growth, bone age, bone mineral density, physical signs of pubertal maturation in patients who are pre- or peri-pubertal (<Tanner 4). This will be done by bone age x-rays, bone density scans and hormones associated with growth and pubertal development in both male and female pediatric patients at the beginning of entry into the study and then every 12 cycles or sooner if the patient comes off of study ~~or if any abnormalities are noted.~~

Incisor teeth: White (discolored) incisor teeth were noted during clinical observations in male rats and correlated histopathologically with minimal to moderate ameloblast degeneration/necrosis and/or minimal to mild pigmented mononuclear cell infiltrate. Minimal to mild neutrophilic inflammation of the incisor tooth was also identified in animals euthanized in moribund condition. The white discoloration of teeth was reversible and correlated with a lack of ameloblast degeneration/necrosis at the end of the non-dosing period. Incisor tooth effects were not identified in dogs. In Study 1, dental abnormalities/tooth discoloration will be assessed by the care provider noted on physical exam at each study site. Any issues will be reported to Pfizer and appropriate referrals will be recommended.

Glucose dysregulation: Alterations in glucose metabolism as evidenced by increased glycemia and/or glucosuria was identified the 15- and 27-week toxicity studies conducted in growing rats (2 months upon study start). Outcomes from growing and aged rats and the scientific literature suggest the potential for palbociclib to cause pancreatic islet beta cell loss and subsequent dysregulation of glucose in very young children. The risk of glucose dysregulation, pancreatic toxicity, and secondary effects on the eye have been identified. ~~In The protocol for Study 1 will contain provisions for monitoring, glucose,~~ at the beginning of every cycle and HgbA1c levels, every 4 cycles, ~~will be monitored~~ to assess for glucose dysregulation. If abnormalities are found, referrals to appropriate specialists ~~will may~~ be recommended as per local clinical standard of care.

The most common adverse reactions (incidence $\geq 10\%$) occurring in studies supporting approval of palbociclib for use in combination with other agents in patients with advanced or metastatic breast cancer were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, alopecia, diarrhea, thrombocytopenia, rash, vomiting, decreased appetite, asthenia, and pyrexia.

Across Studies A5481001, A5481002 and A5481010, which investigated single-agent palbociclib in adult patients with a variety of tumor types, the most frequently reported treatment-emergent adverse events (TEAEs) ($\geq 20\%$ of patients) of any grade, regardless of causality were fatigue (48.5% of patients), neutropenia (42.7%), nausea (33%), diarrhea (32%), anemia (30.1%), constipation (26.2%), and decreased appetite (20.4%). The most frequently reported TEAEs ($\geq 20\%$ of patients) of any grade that were considered to be related to the study treatment were fatigue (41.7% of patients), neutropenia (40.8%), diarrhea (24.3%), and nausea and anemia (23.3% each).

The most frequently reported Grade 3 TEAEs irrespective of causality across the single-agent studies were neutropenia (21.4% [22 patients]), anemia (9.7% [10 patients]), fatigue (5.8% [6 patients]), leukopenia, thrombocytopenia and dyspnea (4.9% each [5 patients]). Twenty (20 [19.4%]) reports of Grade 3 neutropenia were considered to be related to study treatment. All reports of Grade 3 leukopenia and thrombocytopenia were considered related to study treatment.

The most frequently reported Grade 4 TEAEs across the single-agent studies were neutropenia (5.8% [6 patients]; all considered to be related to the study treatment) and thrombocytopenia (2.9% [3 patients]; considered to be related to study treatment for 2 patients). Grade 4 leukopenia was reported for 2 patients (1.9%) and Grade 4 anemia, pulmonary embolism, blood uric acid increased, hemoglobin and hyperglycemia for 1 patient each (1.0%). Grade 5 events were reported for 8 patients (7.8%) which included disease progression (4.9% [5 patients]), cardiac arrest (1.9% [2 patients]), and failure to thrive (1.0% [1 patient]). No Grade 5 event was considered to be related to palbociclib.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.
- *Drug information:*
 - *Dosage form:*
Palbociclib will be utilized either as an oral solution formulation (concentration 25 mg/mL) or capsule (75, 100, or 125 mg capsule strengths). The oral solution has been developed for pediatric patients and patients potentially unable to swallow the capsule formulation intact and to provide a more flexible dosing range when based on body surface area.
 - *Route of administration:* Oral

- ***Dosing regimen:***
Palbociclib, TMZ, IRN, TOPO, and CTX will be administered based on body surface area (BSA) dosing. BSA will be calculated by individual investigative site standard methods.

Study 1 (dose escalation) palbociclib+IRN+TMZ:

Escalating doses of palbociclib, starting at 55 mg/m², are to be administered orally once daily on Days 1-14 days followed by a 7-day off-treatment period, with TMZ administered orally once daily at 100 mg/m² on Days 1 to 5 and IRN administered intravenously (IV) at 50 mg/m² over 90 minutes on Days 1 to 5. For patients who cannot swallow TMZ capsules, TMZ can be administered as an IV infusion over 90 minutes. Depending on the safety evaluation of the initial cohort, palbociclib may be de-escalated to 40 mg/m² or escalated up to 115 mg/m².

Study 1 (dose determination) palbociclib+TOPO+CTX:

Palbociclib will be administered daily for 14 days followed by 7 days off in 3-week cycles. The starting dose will be 75 mg/m² which is the MTD for palbociclib in combination with IRN and TMZ as determined in the dose escalation part of Study 1. This dose is considered the Maximal Administered Dose (MAD) for palbociclib in combination with TOPO and CTX and no dose escalation for this combination is planned. If the MAD is associated with excessive toxicity, palbociclib dose de-escalation will be allowed to the next lower dose level of 55 mg/m².

Palbociclib will be administered with TOPO at 0.75 mg/m² IV over 30 minutes and CTX at 250 mg/m² IV over 30-60 minutes on Days 1-5 of each 21-day cycle.

Study 1 (dose expansion and tumor-specific cohorts) palbociclib+IRN+TMZ:

Palbociclib will be administered daily for 14 days followed by 7 days off in 3-week cycles. The starting dose level in dose expansion will be 75 mg/m² which has been determined as the MTD for palbociclib in combination with IRN+TMZ in the dose escalation part of Study 1. The dose level in tumor-specific cohorts will be the RP2D of palbociclib in combination with IRN+TMZ as confirmed in dose expansion.

On the basis of the calculated BSA, 5 mg, 20 mg, and 100 mg, capsules of TMZ will be used to generate the treatment dose of 100 mg/m² orally. TMZ will be administered on Days 1-5 in 3-week cycles. Patients unable to swallow the capsules should receive an IV formulation of TMZ, administered according to the product information.

IRN will be administered at 50 mg/m² IV on Days 1-5 in 3-week cycles.

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Study 1 (dose expansion and tumor specific cohorts) palbociclib+TOPO+CTX:

Palbociclib will be administered daily for 14 days followed by 7 days off in 3-week cycles. The calculated dose for dose expansion will be determined based on the potential RP2D for palbociclib in combination with TOPO+CTX in the dose determination part of **Study 1**. The dose level in tumor-specific cohorts will be the RP2D of palbociclib in combination with TOPO+CTX as confirmed in dose expansion.

TOPO will be dosed at 0.75 mg/m² IV over 30 minutes (±10%) on Days 1-5 of each 21-day cycle.

CTX will be dosed at 250 mg/m² IV over 30-60 minutes (±10%) on Days 1-5 of each 21-day cycle.

Subcutaneous G-CSF (5 µg/kg/dose daily) will be mandatory in the combination of palbociclib with TOPO+CTX starting Cycle 1. The G-CSF should be initiated 24-48 hours after the administrations of TOPO and CTX are completed and should be continued until the expected neutrophil nadir is passed and the neutrophil counts has recovered to minimum of ANC ≥1000/mm³. G-CSF must be stopped 24 hours prior to the next treatment cycle. At the discretion of the investigator the daily G-CSF (filgrastim) can be substituted by PEG-filgrastim in a standard weight-based dosing for pediatric patients. PEG-filgrastim should be initiated 24-48 hours after the administrations of TOPO and CTX are completed and must be stopped 14 days prior to the next treatment cycle.

Study 1 (Phase 2) palbociclib+IRN+TMZ vs IRN+TMZ:

Palbociclib will be administered orally once daily for 14 days followed by 7 days off. The dose administered will be determined based on the RP2D confirmed from Study 1 Phase 1 dose expansion part.

On the basis of the calculated BSA, 5-mg, 20-mg, 100-mg capsules of TMZ may be used to generate the treatment dose of 100 mg/m² orally on Days 1-5 of each 21-day cycle. Patients unable to swallow the capsules should receive an IV formulation of TMZ, administered according to the product information.

IRN will be dosed at 50 mg/m² IV on Days 1-5 of each 21-day cycle.

Study 3

Palbociclib is taken orally once daily for 21 days followed by 1 week off treatment for a course of 28 days. Escalating doses of palbociclib will be given starting at 50 mg/m². Depending on the safety evaluation of the initial cohort, palbociclib may be escalated to 75 mg/m² or escalated up to 95 mg/m².

Study 4

Palbociclib is taken orally once daily at 75 mg/m² for 21 days followed by 1 week off treatment for a course of 28 days.

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

- 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
- 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
- 3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*

Study 1 Phase 1

The Dose Escalation Part employs a Rolling 6 design to determine the MTD for the combination of palbociclib+TMZ+IRN in children, adolescents, and young adults with solid tumors. The MTD is defined as the highest dose level

at which <33% of a minimum of 6 evaluable patients experience a DLT during Cycle 1 of treatment.

The dose determination part employs a modified Rolling 6 design to guide dose de-escalation and to determine the dose proceeding to dose expansion to confirm the RP2D for the combination of palbociclib+TOPO+CTX in children, adolescents, and young adults with solid tumors.

The starting dose of palbociclib in combination with TOPO+CTX is the MTD determined in the IRN and TMZ combination (75 mg/m²). This dose is considered the MAD and no further dose escalation is planned. If <33% of a minimum of 6 evaluable patients experience a DLT at the MAD, the dose will proceed to dose expansion to be confirmed as the RP2D. If ≥33% of evaluable patients experience a DLT, dose will be de-escalated to the next lower dose level of 55 mg/m². If a minimum of 6 evaluable patients have been treated at this dose level and <33% experience a DLT, the dose will proceed to dose expansion to further confirm the RP2D.

Once the MTD for palbociclib+IRN+TMZ and a potential RP2D for palbociclib+TOPO+CTX have been determined, the respective Dose Expansion Cohort will enroll a minimum of 12 patients for each combination with any solid tumor type to further evaluate the safety and confirm the RP2D and obtain preliminary assessment of antitumor activity in this overall patient population.

Tumor-specific cohorts (non-EWS for the combination of palbociclib with IRN and TMZ) of up to 21 patients each within each combination may also be opened pending observation of antitumor activity observed in the dose finding and dose expansion parts of the study. A Simon's 2-stage optimal design ([Table 1](#)) will be used for each of the opened tumor-specific cohorts. Under the null hypothesis of a true response rate that does not exceed 33%, the two-stage design will control one-sided type I error to be approximately 0.10. If the true response rate is at least 58%, type II error will be no more than 0.20. In the first stage, 7 patients will be enrolled in each cohort. Of note, any patients with the specific tumor treated in the dose finding and dose expansion parts of the study will be counted as part of the 7 patients of the first stage of the tumor-specific cohort. If there are 2 confirmed objective responses in these 7 patients, the study will be stopped for ineffectiveness. If there are 6 or more confirmed objective responses in these 7 patients, the study will be stopped for effectiveness. Otherwise, 14 additional patients will be enrolled for a total of 21 in each tumor-specific cohort. The null hypothesis will be rejected if 10 or more confirmed objective responses are observed in 21 patients.

Objective response (OR) is defined as a complete response (CR) or partial response (PR) according to RECIST v. 1.1 or modified RANO for CNS

malignancies, and the objective response rate (ORR) is calculated as the percentage of patients with a best overall response of CR or PR. OR is defined as a CR, PR or minor response (MR) according to INRC for neuroblastoma, and the ORR is calculated as the percentage of patients with a best overall response of CR, PR or MR. Confirmation of the response is required. Patients who die, progress, or permanently discontinue study treatment for any reason after being treated prior to documented response will be included in the analysis as non-responders. ORR with confidence intervals will be provided.

Safety analyses will be descriptive in nature. Pooled PK data in the Dose Escalation Part and Dose Expansion Cohort from Phase 1 and Phase 2 will be reported by predefined age groups.

Study 1 Phase 2

Once the RP2D is confirmed for the combination of palbociclib with IRN and TMZ, the Phase 2 portion of Study 1 will be initiated with the primary objective being to compare the efficacy of palbociclib in combination with IRN and TMZ to IRN and TMZ chemotherapy alone in the treatment of children, adolescents, and young adults with recurrent or refractory EWS. The primary endpoint is event-free survival (EFS) based on investigator assessment. Additional secondary endpoints include OR, PFS, OS, PET-CT response after Cycle 4, safety, PK, QOL and days of hospitalization.

The primary endpoint of EFS is defined as the time from randomization to first event, where an event includes:

- Progression without achieving a response (CR or PR) or
- Recurrence (following a response) or
- Diagnosis of second malignancy or
- Death without progression or recurrence

Patients last known to be event-free will be censored at the date of the last objective disease assessment that verified lack of disease progression, recurrence or second malignancy.

The sample size for the Phase 2 portion of the study is determined based on the assumptions that median EFS for patients receiving IRN and TMZ chemotherapy alone in the treatment of recurrent and refractory EWS is 4.7 months (McCabe et al, 2020) and an improvement to median EFS of 8.1 months (corresponding to a HR=0.58) for palbociclib in combination with IRN and TMZ is considered clinically significant. A total of approximately 50 EFS events are required in the two treatment arms of the study based on a 2:1 randomization to have at least 80% power to detect a hazard ratio of 0.58 in favor of palbociclib plus IRN and TMZ arm using a 1-sided log-rank test at a significance level of 0.20. Assuming a non-uniform accrual accomplished over

a 25-month period and follow-up for about 6 months after the last patient is enrolled, a total sample size of approximately 75 patients (~50 patients in the palbociclib in combination with IRN and TMZ arm and ~25 patients in the IRN and TMZ chemotherapy alone arm) is required. It is anticipated that a minimum of 60% of the patients enrolled in each arm will be pediatric patients (age ≥ 2 and < 18 years old). Randomization will be stratified using block randomization by type and time of current disease recurrence (primary refractory or 1st recurrence < 2 yrs versus 1st recurrence ≥ 2 yrs or 2nd or greater recurrence).

An interim futility analysis will be conducted to allow for early stopping of the study due to futility/no signal of activity based on the primary endpoint of EFS. The analysis will be performed after approximately 30 EFS events (~60% of total events expected) have been documented. If the 1-sided p-value is > 0.4287 ($Z > -0.1796$) at the interim analysis, the Phase 2 portion of the study will be terminated early for lack of efficacy.

The primary analysis of EFS based on investigator assessment will be summarized in the full analysis set using the Kaplan-Meier method and displayed graphically where appropriate. The median EFS and corresponding 2-sided 95% CI will be provided. A stratified log-rank test will be used to compare EFS between the two treatment arms. The hazard ratio and associated 2-sided 95% CI will be estimated using the stratified Cox proportional hazards model.

Study 3

A Rolling-6 Phase 1 design is used to estimate the MTD, where dose escalations are planned in cohorts of 2 to 6 patients. The MTD, defined as the highest dose level at which 6 patients have been treated with at most 1 patient experiencing a DLT and the next higher dose level has been determined to be too toxic, will be determined separately in less-heavily pre-treated patients (stratum I) and heavily pre-treated patients (stratum II), respectively. Once the MTD has been estimated or the RP2D has been determined, 6 additional patients will be treated at that dose level to better describe the toxicity profile of palbociclib. Adverse event data will be summarized in stratum-specific tables, which will incorporate dose, attribution, and grade information. Any objective responses observed in this trial will be described by dose and by histology.

Study 4

APEC1621I will require a minimum of 204 evaluable patients and a maximum of 49 patients, allowing for 15% inevaluability.

APEC1621I will evaluate a primary cohort of 20 mutation-matched ("biomarker positive") evaluable patients of any histology for the primary study aim of determining the objective response rate (CR/PR) to the agent. Using

an A'Hern design with $\alpha=10\%$, a sample of $N=20$ will provide 90% power to detect an improvement in response rate from 5%, if the treatment is ineffective, to 25% if the targeted therapy is sufficiently effective to warrant further study. If there are at least 3 responses out of 20 in the primary cohort, the biomarker/therapy match will be deemed a success.

If ≥ 3 patients in the primary cohort with the same histology show signs of objective response (CR/PR), a histology-specific biomarker positive expansion cohort will open after the primary cohort is completed to up to 7 evaluable patients for a total sample size of 10 evaluable biomarker positive patients with that histology. The Sponsor will open up to 3 such expansion cohorts for biomarker positive patients. Note that this can only happen if the response rate in the primary cohort is at least 45% (9/20), and there cannot be more than 21 additional evaluable patients in total for these expansion cohorts.

Toxicity tables will be constructed to summarize the observed incidence by type of toxicity and grade. Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).

- *Labeling that may result from the study(ies):* You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that palbociclib is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).
- *Format and types of reports to be submitted:* You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should report one of the following designations: Hispanic/Latino or Not Hispanic/Latino. ~~If you choose to use other categories, you should obtain agency agreement.~~

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The studies may also use one of the following additional categories for race, as applicable: Not reported, Multiracial, or Unknown.

The studies may also use one of the following additional categories for ethnicity, as applicable: Not reported or Unknown.

If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the guidance addendum.¹ You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document “Study Data Specifications,” which is posted on FDA.gov² and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- **Timeframe for submitting reports of the study(ies):** Reports of the above studies must be submitted to the Agency on or before December 5, 2025. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.
- **Response to Written Request:** Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>

² <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf>

must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies) but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the FD&C Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

- (1) the type of response to the Written Request (i.e. complete or partial response);
- (2) the status of the application (i.e. withdrawn after the supplement has been filed or pending);
- (3) the action taken (i.e. approval, complete response); or
- (4) the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.³

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will

³ <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm>

be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the PHS Act, you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found on the Clinical Trials website.⁴

If you have any questions, contact Maritsa Stephenson, Regulatory Project Manager, at Maritsa.Stephenson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Martha Donoghue, M.D.
Acting Associate Director, Pediatric Oncology
Office of Oncologic Diseases
Center for Drug Evaluation and Research

⁴ www.ClinicalTrials.gov



IND 135210
NDA 207103

WRITTEN REQUEST – AMENDMENT #3

Pfizer, Inc.
Attention: Lisa Rysso-DeMaggio, BS, RAC
Director, Pfizer Global Regulatory Strategy
10646 Science Center Dr.
San Diego, CA 92121

Dear Ms. Rysso-DeMaggio:

Please refer to your correspondence dated October 7, 2024, January 25, 2025, and February 4, 2025, requesting changes to FDA's July 3, 2018, Written Request for pediatric studies for Ibrance (palbociclib).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on July 3, 2018, and as amended on February 2, 2021, and September 23, 2021, remain the same. (Text added is underlined and text deleted is strikethrough).

BACKGROUND:

These studies will investigate the potential use of palbociclib in the treatment of recurrent/refractory pediatric solid tumors, including Ewing sarcoma (EWS).

Palbociclib (PD-0332991) is a highly selective, reversible, small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6, administered orally. Cyclin D1 and CDK4/6 are downstream of multiple signaling pathways which lead to cellular proliferation. Through inhibition of CDK4/6, palbociclib reduces cellular proliferation by blocking progression of the cell from G1 into S phase of the cell cycle. There is interest in CDK 4/6 inhibitors given the mechanism of action and their effect on cell proliferation which is potentially applicable to many types of adult and pediatric cancers. Palbociclib (IBRANCE®) is currently indicated for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer (MBC) in combination with an aromatase inhibitor as initial endocrine-based therapy, or fulvestrant in patients with disease progression following endocrine therapy. Since breast cancer does not occur in children or adolescents, the benefit of palbociclib demonstrated in HER2-, HR+ MBC cannot be extrapolated to alternate tumor types in the pediatric setting at this time. However, dysregulated cyclin D-CDK4/6 activity has been implicated as a regulator of cell cycle progression in some pediatric cancers, such as neuroblastoma, rhabdoid tumor, medulloblastoma, EWS and RMS.

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According to the American Cancer Society, EWS accounts for 1% of all childhood tumors, with an estimated 225 children and teens diagnosed each year in North America (American Cancer Society, 2017a). Recurrent EWS develops in 30%-60% of children, depending on treatment regimen and study population. Recurrent/metastatic EWS has a poor prognosis, with less than 20% 5-year overall (Stahl et al, 2011). There is no standard second-line treatment. The choice of regimen depends on the type of relapse (local versus metastatic disease), time to relapse, the patient's general condition, and previous first-line treatment.

Studies of palbociclib in neonates are not required because children < 2 years of age are excluded from the studies in this Written Request since relapsed/refractory EWS is unlikely to occur in infants and young children. As well, children < 2 years of age are excluded from the clinical development plan of palbociclib due to the possible risk of them developing diabetes based on nonclinical toxicity data.

To obtain needed pediatric information on palbociclib, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

Additional Background Information Influencing Proposed Studies and Endpoints

The original pediatric Written Request included Study 2, which was designed to add a randomized component to the rEECur study to assess the antitumor activity of palbociclib in combination with a standard backbone chemotherapy regimen after sufficient information was obtained in Study 1 to support the safety and antitumor activity of palbociclib in Study 1. The rEECur study, conducted by the University of Birmingham (Sponsor) and the EuroEwing Consortium (EEC), is an ongoing multi-stage, multi-arm, international, randomized controlled trial in patients with recurrent and primary refractory Ewing sarcoma evaluating 4 chemotherapy regimens [gemcitabine (GEM)+docetaxel (DOX), irinotecan (IRN)+temozolomide (TMZ), topotecan (TOPO)+cyclophosphamide (CTX), high-dose ifosfamide (IFOS)], with the goal of identifying two chemotherapy arms to continue to a Phase 2 comparison.

In March 2020, results from the second interim assessment of the rEECur Study suggested that the clinical activity of the IRN+TMZ and TOPO+CTX combinations or single-agent IFOS were comparable; the observed overall response rate (ORR) was 20% in the IRN+TMZ arm versus 23% in the IFOS and TOPO+CTX combined arms and the median progression-free survival (PFS) was 4.7 months for IRN+TMZ versus 5.3 months for IFOS and TOPO+CTX combined (McCabe et al, 2020). The EEC also reported that the response rate in this clinical trial at the second interim assessment timepoint did not correlate well with the PFS and OS outcomes in patients with recurrent and/or primary refractory EWS (Wheatley et al, 2020). Considering the lack of a clear correlation between ORR and survival parameters and the minimal rate of second malignancies in the studied patient population within

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the rEECur trial to date, the EEC changed the primary endpoint of the Phase 2 portion of rEECur to EFS. The IRN+TMZ chemotherapy arm was subsequently discontinued from the rEECur study and in February 2021, the Written Request was amended to change the backbone in Study 2 to TOPO+CTX. Amendment #1 incorporated additional changes to Study 2 to specify collection of sparse PK samples for palbociclib, topotecan, and cyclophosphamide in all pediatric patients (ages > 2 to < 18 years). Amendment #1 also revised Study 1 to include TOPO+CTX as an additional backbone for combination dose escalation with palbociclib based on the results from Study 2, to specify a minimum number of patients to be enrolled in each age group, and state that tumor specific cohorts may be opened as warranted based on signals of anti-tumor activity observed in the dose finding and dose expansion parts of Study 1.

In March 2021, the EEC temporarily suspended recruitment to the TOPO+CTX arm due to observed differences, unrelated to safety, between the outcomes of patients randomized to the TOPO+CTX and high dose IFOS arms. Due to challenges and delays in introducing a palbociclib/backbone chemotherapy combination into the rEECur study, the Written Request was amended again in September 2021 to remove Study 2 and add a randomized component with a primary EFS efficacy endpoint to Study 1 comparing palbociclib in combination with IRN+TMZ to IRN+TMZ alone in lieu of conducting a separate randomized trial for feasibility (Amendment 2). The revision to Study 1 was designed in conjunction with advice and support from the Children's Oncology Group (COG). COG agreed that IRN+TMZ is standard of care for this population in the United States and may have less toxicity than TOPO+CTX or high-dose IFOS.

The WR was most recently amended in February 2025 to include edits for clarity and brevity, minor revisions related to categorization of race and ethnicity, updates based on Study 1 completion following conduct of a planned interim analysis, and clarifications related to the submission of study reports (Amendment #3). Results of a planned analysis of Study 1 Stage 1 tumor specific cohort indicated that palbociclib in combination with TOPO and CTX is ineffective for patients with recurrent or refractory neuroblastoma (NB); therefore, additional enrollment of the NB tumor specific will not occur and Study 1 tumor specific cohort will not proceed to Stage 2.

- *Nonclinical study(ies):*

Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*

Study 1 (Study A5481092): A Phase 1/2 open-label study to evaluate palbociclib in combination with TMZ and IRN and palbociclib in combination with TOPO and CTX in children, adolescent, and young adult patients with relapsed or refractory solid

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tumors. The non-randomized Phase 1 portion of the study will evaluate the safety, pharmacokinetics (PK) and antitumor activity of palbociclib in combination with TMZ and IRN and palbociclib in combination with TOPO and CTX in patients with relapsed or refractory solid tumors. The randomized Phase 2 portion of the study will further evaluate the efficacy, safety, and PK of palbociclib in combination with IRN and TMZ in children, adolescents, and young adults with recurrent or refractory EWS.

In the Phase 1 portion of Study 1, the dose-escalation/determination part will include pediatric patients with recurrent or refractory solid tumors. The dose expansion portion for each combination will first enroll and treat a minimum of 12 patients with any recurrent or refractory solid tumor type to confirm the palbociclib recommended Phase 2 dose (RP2D) for each combination. If 2 or more patients from the dose escalation/determination parts and/or dose expansion cohorts from either combination show an objective response within a specific tumor type (such as neuroblastoma, RMS, rhabdoid tumors, or medulloblastoma), a tumor-specific cohort will be opened to further evaluate anti-tumor activity of the respective combination within the specific cancer subtype.

If tumor-specific cohorts with palbociclib in combination with either TMZ and IRN or TOPO and CTX are opened, then a modified Simon's 2-stage optimal design will be followed with the decision rules as shown below. Under the null hypothesis of a true ORR that does not exceed 33%, the 2-stage optimal design will control 1-sided type I error to be approximately 0.10. If the true ORR is at least 58%, type II error will be no more than 0.20 (i.e., at least 80% power) ([Table 1](#)).

Table 1. Modified Simon's 2-Stage Optimal Design Decision Rules for Other Tumor Specific Cohorts

	Cumulative Number of Responses^a	Decision
Stage 1: Enroll a total of 7 patients^b	2	Terminate enrollment- agent ineffective
	3 – 5	Inconclusive-proceed to Stage 2
	6 ^c	Terminate enrollment- agent effective
Stage 2: Enroll 14 additional patients (N=21 total)	9 or less	Agent ineffective
	10 or more	Agent effective

Table 1. Modified Simon's 2-Stage Optimal Design Decision Rules for Other Tumor Specific Cohorts

	Cumulative Number of Responses^a	Decision
a.	Assumption based on an objective response rate of 33% for IRN/TMZ or TOPO/CTX and 58% for palbociclib/IRN/TMZ or palbociclib/TOPO/CTX, respectively	
b.	Evaluated patients will include the 2 objective responses observed and any other patients with the same tumor type during the dose escalation and dose determination part and dose expansion cohort of the study.	
c.	Lower bound of the Wilson's 2-sided 80% CI is greater than 62%	

The open-label, randomized Phase 2 portion of Study 1 will evaluate the efficacy, safety, PK and pharmacodynamic (PD) activity of palbociclib in combination with IRN and TMZ versus IRN and TMZ alone in children, adolescent, and young adult patients with recurrent or refractory EWS. Of note, although patients with EWS can enroll into the dose escalation part and the dose expansion cohort of the study for palbociclib in combination with IRN and TMZ, a tumor specific cohort for EWS will not be opened in Study 1 for this combination since the randomized Phase 2 portion will enroll patients with EWS to evaluate efficacy of palbociclib in combination with IRN and TMZ.

The Phase 2 portion of Study 1 will randomize up to approximately 75 eligible patients (age ≥ 2 and < 21 years) with recurrent or refractory EWS, using 2:1 randomization, stratified using block randomization by type and time of current disease recurrence (primary refractory or 1st recurrence < 2 years versus 1st recurrence ≥ 2 years or 2nd or greater recurrence). It is expected approximately 75% of the patients will be pediatric patients (age ≥ 2 and < 18 years). A total of approximately 50 EFS events are required in the two treatment arms of the study to have at least 80% power to detect a hazard ratio of 0.58 in favor of palbociclib in combination with IRN and TMZ arm using a 1-sided log-rank test at a significance level of 0.20. The study is considered hypothesis generating only.

Study 3: An open-label, Phase 1, dose escalation study to evaluate the safety and pharmacokinetics of palbociclib in pediatric patients with retinoblastoma protein 1 (Rb1)- positive recurrent, progressive, or refractory central nervous system (CNS) tumors (Study PBTC-042)

Study 4: An open-label Phase 2 trial to evaluate single-agent palbociclib in pediatric patients with tumors harboring activating alterations in cell cycle genes (Study APEC1621I).

Efficacy in pediatric patients ages ≥ 2 to < 18 years with recurrent or refractory EWS in the Phase 2 portion of **Study 1** will be supported by data in young adult patients (ages ≥ 18 to < 21 in **Study 1**), given the rarity of EWS in young pediatric patients and

the fact that EWS occurs throughout adolescence and young adulthood. Most diagnoses of EWS occur in patients >10 years of age. A minimum of 60% of patients per arm enrolled in Study 1 Phase 2 must be <18 years of age.

The confirmation of the recommended phase 2 dose (RP2D) from the Phase 1 portion of **Study 1** must be completed before initiating the open-label, randomized Phase 2 portion of **Study 1**.

- *Objective of each study:*

Study 1

Phase 1

Dose Escalation Part:

- To estimate MTD for the combination of palbociclib+TMZ+IRN in children, adolescents and young adults with recurrent or refractory solid tumors
- To characterize the safety profile of palbociclib combined with TMZ and IRN
- To describe the PK of palbociclib, TMZ, and IRN in children, adolescents and young adults when given in combination
- To evaluate the preliminary anti-tumor activity of palbociclib combined with TMZ and IRN

Dose Determination Part:

- To determine the potential RP2D for palbociclib in combination with TOPO and CTX in children, adolescents, and young adults with recurrent or refractory solid tumors.
- To characterize the safety profile of palbociclib combined with TOPO and CTX.
- To describe the PK of palbociclib, TOPO, and CTX in children, adolescents, and young adults with recurrent or refractory solid tumors when given in combination
- To evaluate the preliminary anti-tumor activity of palbociclib combined with TOPO and CTX.

Dose Expansion Parts and Tumor-Specific Cohorts:

- To evaluate the safety and confirm the RP2D for the combination of palbociclib+TMZ+IRN and the combination of palbociclib+TOPO+CTX in children, adolescents and young adults with recurrent or refractory solid tumors, which may include RMS, EWS, and other disease-specific solid tumors.
- To evaluate the preliminary anti-tumor activity of palbociclib combined with TMZ and IRN and palbociclib combined with TOPO and CTX in children, adolescents and young adults with recurrent or refractory solid tumors, including disease-specific solid tumors.
- To describe the PK of palbociclib, TMZ and IRN and of palbociclib, TOPO and CTX in children, adolescents and young adults with recurrent or refractory solid tumors when given in combination.

Phase 2

- To compare the efficacy of palbociclib plus TMZ and IRN versus TMZ and IRN alone in the treatment of patients with recurrent or refractory EWS
- To characterize the toxicity, and safety of the combination of TMZ and IRN plus or minus palbociclib
- To describe the PK of palbociclib, TMZ, and IRN in patients with recurrent or refractory EWS when given in combination
- To assess the impact of the combination of palbociclib with TMZ and IRN treatment on the quality of life (QoL) of patients with recurrent or refractory EWS.

Study 3

- To determine the MTD/RP2D and describe toxicities related to palbociclib in children with Rb1-positive recurrent, progressive or refractory primary CNS tumors
- To determine plasma PK of palbociclib in children with Rb1-positive recurrent, progressive or refractory primary CNS tumors
- To record preliminary evidence of efficacy of palbociclib in children with recurrent CNS tumors

Study 4

- To determine the objective response rate (ORR) in pediatric patients treated with palbociclib with advanced solid tumors (including CNS tumors), non-Hodgkin lymphomas or histiocytic disorders that harbor activating genetic alterations in cell cycle genes
- To estimate progression free survival (PFS) in pediatric patients treated with palbociclib with advanced solid tumors (including CNS tumors), non-Hodgkin lymphomas or histiocytic disorders that harbor activating genetic alterations in cell cycle genes
- To obtain information about the tolerability of palbociclib in pediatric patients with relapsed/refractory cancer
- *Patients to be Studied:*

Study 1

Age ≥ 2 years and < 21 years at the time of study entry

Phase 1:

Dose Escalation Part (palbociclib in combination with IRN and TMZ): A minimum of 6 patients to a maximum of 24 DLT evaluable patients with recurrent or refractory solid tumors

Dose Determination Part (palbociclib in combination with TOPO and CTX): A minimum of 6 to a maximum of 12 DLT evaluable patients with recurrent or refractory solid tumors

Dose Expansion Parts: A minimum of 12 patients (for each palbociclib combination) with recurrent or refractory solid tumors with the possibility of opening additional tumor-specific cohorts (maximum of 21 patients per cohort) if anti-tumor activity is observed.

Phase 2:

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 fertility will be conducted; fewer patients may be enrolled if the fertility criteria are met.

Study 3

A maximum of 55 patients with Rb1-positive recurrent, progressive, or refractory primary CNS tumors ≥ 4 years and ≤ 21 years of age.

Study 4

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.

Pooled Pharmacokinetic Analysis

Adequate pharmacokinetic (PK) samples of palbociclib will be collected in **Studies 1** and **3** in order to allow for determination of palbociclib PK parameters by non-compartmental analyses. PK sample collections of palbociclib will be included in the Phase 2 portion of **Study 1**, which will contribute to a pooled POP-PK analysis using pooled data from **Studies 1** and **3** to determine population PK parameters, such as the apparent clearance (CL/F) and volume of distribution (Vd/F) of palbociclib in pediatric patients. As the data allow, exposure-response relationships for safety and efficacy endpoints of interest may also be explored.

While the Sponsor should attempt to enroll 6 patients with each triplet combination, given the rarity of pediatric cancer patients in specified age ranges, a minimum of 6 patients treated with the combination of either palbociclib+TMZ+IRN or palbociclib+TOPO+CTX in **Study 1** will be enrolled in each of the following age groups: ≤ 6 years old, >6 years but <12 years, and ≥ 12 years old but <18 years to provide for a PK analysis by stratified age group. The PK sample collection plan for the patients contributing to these minimums of 6 patients per the 3 stratified age groups should be sufficient to allow for determination of palbociclib PK parameters by non-compartmental analyses.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

Study 1

Phase 1:

Dose Escalation/Dose Determination Parts:

- The primary endpoint will be first-cycle dose-limiting toxicities (DLTs).

Dose Expansion Parts and Tumor-Specific Cohorts:

- The primary endpoints are:
 - Adverse Events as characterized by type, frequency, severity, as graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03), laboratory test data, electrocardiogram parameters, and vital signs
 - Objective tumor response (OR) as assessed using Response Evaluation Criteria in Solid Tumor (RECIST version 1.1) or modified Revised Assessment in Neuro Oncology (RANO) for CNS malignancies or International Neuroblastoma Response Criteria (INRC) criteria for neuroblastoma.
- Secondary endpoints will include:
 - Duration of Response (DOR), PFS, and Overall Survival (OS).
 - PK parameters of palbociclib, TMZ, IRN, TOPO, and CTX: multiple dose $C_{ss,max}$, T_{max} , $AUC_{ss,tau}$, $C_{ss,trough}$, and CL/F, as data permit.

Phase 2:

- The primary endpoint is event-free survival (EFS) based on investigator assessment.
- The secondary endpoints are:
 - Adverse events as graded by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.03 (all SAEs and non-serious AEs Grade ≥ 3 and other select non-serious AEs as defined by the protocol).
 - PK parameters of palbociclib, TMZ, and IRN when used in combination, as data permit
 - Objective response (OR) as assessed by investigator using RECIST version 1.1.
 - PET-CT response after Cycle 4 compared to OR on MRI/CT
 - PFS based on investigator assessment
 - OS
 - QoL at baseline and after 2 and 4 cycles using age-appropriate tools
 - Days of hospitalization

Study 3

- The primary endpoint is DLTs during the first course of treatment.
- The key secondary endpoints are:
 - Adverse Events as graded by NCI CTCAE version 4.03,
 - ORR,
 - Individual PK parameters of palbociclib

Study 4

- The primary endpoint is ORR as assessed by RECIST v1.1.
- The key secondary endpoints are:
 - PFS estimated using the Kaplan-Meier method, and
 - incidence of adverse events assessed by the current version of the NCI CTCAE

- *Known drug safety concerns and monitoring:*

Male reproduction: Effects on male reproductive organs (testis, epididymis, prostate, seminal vesicle) were observed in rats and dogs. The incidence and severity of testicular and epididymal findings were dose-related (minimal to severe) and often correlated with decreases in testicular and epididymal weights. Testicular degeneration produced by palbociclib was partially reversible after 12 weeks of dose-free period and is consistent with CDK inhibition and alteration of cell cycle kinetics, given the rapid and continuous cycling of germ cells. In Study 1, sexual development effects will be monitored by study sites per protocol. Of note, patients enrolled into this study would have had previously received gonadotoxic therapy and will be difficult to isolate the effect of palbociclib versus prior therapies.

Bone: Effects on bone observed in male rats consisted of a mild to moderate decrease in trabeculae of the femur, characterized by decreased thickness of the physis, decreased or segmental loss of primary and secondary spongiosa, and/or decreased trabeculae within the metaphysis. No recovery was observed in the femur where mild to marked decreased bone formation was observed. There were no palbociclib-related bone effects in female rats at higher doses and exposures or in dogs at any dose.

The protocol for Study 1 will include provisions for monitoring the effects of treatment with palbociclib on parameters of bone metabolism, growth, and pubertal development in patients who are pre- or peri-pubertal (<Tanner 4). This will be done by bone age x-rays, bone density scans and hormones associated with growth and pubertal development in both male and female pediatric patients at the beginning of entry into the study and then every 12 cycles or sooner if the patient comes off of study.

Incisor teeth: White (discolored) incisor teeth were noted during clinical observations in male rats and correlated histopathologically with minimal to moderate ameloblast

degeneration/necrosis and/or minimal to mild pigmented mononuclear cell infiltrate. Minimal to mild neutrophilic inflammation of the incisor tooth was also identified in animals euthanized in moribund condition. The white discoloration of teeth was reversible and correlated with a lack of ameloblast degeneration/necrosis at the end of the non-dosing period. Incisor tooth effects were not identified in dogs. In Study 1, dental abnormalities noted on physical exam will be reported to Pfizer and appropriate referrals will be recommended.

Glucose dysregulation: Alterations in glucose metabolism as evidenced by increased glycemia and/or glucosuria was identified the 15- and 27-week toxicity studies conducted in growing rats (2 months upon study start). Outcomes from growing and aged rats and the scientific literature suggest the potential for palbociclib to cause pancreatic islet beta cell loss and subsequent dysregulation of glucose in very young children. The risk of glucose dysregulation, pancreatic toxicity, and secondary effects on the eye have been identified. The protocol for Study 1 will contain provisions for monitoring glucose at the beginning of every cycle and HgbA1c levels every 4 cycles, to assess for glucose dysregulation. If abnormalities are found, referrals to appropriate specialists may be recommended as per local clinical standard of care.

The most common adverse reactions (incidence $\geq 10\%$) occurring in studies supporting approval of palbociclib for use in combination with other agents in patients with advanced or metastatic breast cancer were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, alopecia, diarrhea, thrombocytopenia, rash, vomiting, decreased appetite, asthenia, and pyrexia.

Across Studies A5481001, A5481002 and A5481010, which investigated single-agent palbociclib in adult patients with a variety of tumor types, the most frequently reported treatment-emergent adverse events (TEAEs) ($\geq 20\%$ of patients) of any grade, regardless of causality were fatigue (48.5% of patients), neutropenia (42.7%), nausea (33%), diarrhea (32%), anemia (30.1%), constipation (26.2%), and decreased appetite (20.4%). The most frequently reported TEAEs ($\geq 20\%$ of patients) of any grade that were considered to be related to the study treatment were fatigue (41.7% of patients), neutropenia (40.8%), diarrhea (24.3%), and nausea and anemia (23.3% each).

The most frequently reported Grade 3 TEAEs irrespective of causality across the single-agent studies were neutropenia (21.4% [22 patients]), anemia (9.7% [10 patients]), fatigue (5.8% [6 patients]), leukopenia, thrombocytopenia and dyspnea (4.9% each [5 patients]). Twenty (20 [19.4%]) reports of Grade 3 neutropenia were considered to be related to study treatment. All reports of Grade 3 leukopenia and thrombocytopenia were considered related to study treatment.

The most frequently reported Grade 4 TEAEs across the single-agent studies were neutropenia (5.8% [6 patients]; all considered to be related to the study treatment) and thrombocytopenia (2.9% [3 patients]; considered to be related to study

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treatment for 2 patients). Grade 4 leukopenia was reported for 2 patients (1.9%) and Grade 4 anemia, pulmonary embolism, blood uric acid increased, hemoglobin and hyperglycemia for 1 patient each (1.0%). Grade 5 events were reported for 8 patients (7.8%) which included disease progression (4.9% [5 patients]), cardiac arrest (1.9% [2 patients]), and failure to thrive (1.0% [1 patient]). No Grade 5 event was considered to be related to palbociclib.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.
- *Drug information:*
 - *Dosage form:*

Palbociclib will be utilized either as an oral solution formulation (concentration 25 mg/mL) or capsule (75, 100, or 125 mg capsule strengths). The oral solution has been developed for pediatric patients and patients potentially unable to swallow the capsule formulation intact and to provide a more flexible dosing range when based on body surface area.
 - *Route of administration:* Oral
 - *Dosing regimen:*

Palbociclib, TMZ, IRN, TOPO, and CTX will be administered based on body surface area (BSA) dosing. BSA will be calculated by individual investigative site standard methods.

Study 1 (dose escalation) palbociclib+IRN+TMZ:

Escalating doses of palbociclib, starting at 55 mg/m², are to be administered orally once daily on Days 1-14 days followed by a 7-day off-treatment period, with TMZ administered orally once daily at 100 mg/m² on Days 1 to 5 and IRN administered intravenously (IV) at 50 mg/m² over 90 minutes on Days 1 to 5. For patients who cannot swallow TMZ capsules, TMZ can be administered as an IV infusion over 90 minutes. Depending on the safety evaluation of the initial cohort, palbociclib may be de-escalated to 40 mg/m² or escalated up to 115 mg/m².

Study 1 (dose determination) palbociclib+TOPO+CTX:

Palbociclib will be administered daily for 14 days followed by 7 days off in 3-week cycles. The starting dose will be 75 mg/m² which is the MTD for palbociclib in combination with IRN and TMZ as determined in the dose escalation part of Study 1. This dose is considered the Maximal Administered

Dose (MAD) for palbociclib in combination with TOPO and CTX and no dose escalation for this combination is planned. If the MAD is associated with excessive toxicity, palbociclib dose de-escalation will be allowed to the next lower dose level of 55 mg/m².

Palbociclib will be administered with TOPO at 0.75 mg/m² IV over 30 minutes and CTX at 250 mg/m² IV over 30-60 minutes on Days 1-5 of each 21-day cycle.

Study 1 (dose expansion and tumor-specific cohorts) palbociclib+IRN+TMZ:

Palbociclib will be administered daily for 14 days followed by 7 days off in 3-week cycles. The starting dose level in dose expansion will be 75 mg/m² which has been determined as the MTD for palbociclib in combination with IRN+TMZ in the dose escalation part of Study 1. The dose level in tumor-specific cohorts will be the RP2D of palbociclib in combination with IRN+TMZ as confirmed in dose expansion.

On the basis of the calculated BSA, 5 mg, 20 mg, and 100 mg, capsules of TMZ will be used to generate the treatment dose of 100 mg/m² orally. TMZ will be administered on Days 1-5 in 3-week cycles. Patients unable to swallow the capsules should receive an IV formulation of TMZ, administered according to the product information.

IRN will be administered at 50 mg/m² IV on Days 1-5 in 3-week cycles.

Study 1 (dose expansion and tumor specific cohorts) palbociclib+TOPO+CTX:

Palbociclib will be administered daily for 14 days followed by 7 days off in 3-week cycles. The calculated dose for dose expansion will be determined based on the potential RP2D for palbociclib in combination with TOPO+CTX in the dose determination part of **Study 1**. The dose level in tumor-specific cohorts will be the RP2D of palbociclib in combination with TOPO+CTX as confirmed in dose expansion.

TOPO will be dosed at 0.75 mg/m² IV over 30 minutes ($\pm 10\%$) on Days 1-5 of each 21-day cycle.

CTX will be dosed at 250 mg/m² IV over 30-60 minutes ($\pm 10\%$) on Days 1-5 of each 21-day cycle.

Subcutaneous G-CSF (5 µg/kg/dose daily) will be mandatory in the combination of palbociclib with TOPO+CTX starting Cycle 1. The G-CSF should be initiated 24-48 hours after the administrations of TOPO and CTX are completed and should be continued until the expected neutrophil nadir is passed and the neutrophil counts has recovered to minimum of ANC $\geq 1000/\text{mm}^3$. G-CSF must be stopped 24 hours prior to the next treatment cycle. At the discretion of the investigator the daily G-CSF (filgrastim) can be

substituted by PEG-filgrastim in a standard weight-based dosing for pediatric patients. PEG-filgrastim should be initiated 24-48 hours after the administrations of TOPO and CTX are completed and must be stopped 14 days prior to the next treatment cycle.

Study 1 (Phase 2) palbociclib+IRN+TMZ vs IRN+TMZ:

Palbociclib will be administered orally once daily for 14 days followed by 7 days off. The dose administered will be determined based on the RP2D confirmed from Study 1 Phase 1 dose expansion part.

On the basis of the calculated BSA, 5-mg, 20-mg, 100-mg capsules of TMZ may be used to generate the treatment dose of 100 mg/m² orally on Days 1-5 of each 21-day cycle. Patients unable to swallow the capsules should receive an IV formulation of TMZ, administered according to the product information.

IRN will be dosed at 50 mg/m² IV on Days 1-5 of each 21-day cycle.

Study 3

Palbociclib is taken orally once daily for 21 days followed by 1 week off treatment for a course of 28 days. Escalating doses of palbociclib will be given starting at 50 mg/m². Depending on the safety evaluation of the initial cohort, palbociclib may be escalated to 75 mg/m² or escalated up to 95 mg/m².

Study 4

Palbociclib is taken orally once daily at 75 mg/m² for 21 days followed by 1 week off treatment for a course of 28 days.

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

- 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
- 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
- 3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*

Study 1 Phase 1

The Dose Escalation Part employs a Rolling 6 design to determine the MTD for the combination of palbociclib+TMZ+IRN in children, adolescents, and young adults with solid tumors. The MTD is defined as the highest dose level at which <33% of a minimum of 6 evaluable patients experience a DLT during Cycle 1 of treatment.

The dose determination part employs a modified Rolling 6 design to guide dose de-escalation and to determine the dose proceeding to dose expansion to confirm the RP2D for the combination of palbociclib+TOPO+CTX in children, adolescents, and young adults with solid tumors.

The starting dose of palbociclib in combination with TOPO+CTX is the MTD determined in the IRN and TMZ combination (75 mg/m²). This dose is considered the MAD and no further dose escalation is planned. If <33% of a minimum of 6 evaluable patients experience a DLT at the MAD, the dose will proceed to dose expansion to be confirmed as the RP2D. If ≥33% of evaluable patients experience a DLT, dose will be de-escalated to the next lower dose level of 55 mg/m². If a minimum of 6 evaluable patients have been treated at this dose level and <33% experience a DLT, the dose will proceed to dose expansion to further confirm the RP2D.

Once the MTD for palbociclib+IRN+TMZ and a potential RP2D for palbociclib+TOPO+CTX have been determined, the respective Dose Expansion Cohort will enroll a minimum of 12 patients for each combination with any solid tumor type to further evaluate the safety and confirm the RP2D

and obtain preliminary assessment of antitumor activity in this overall patient population.

Tumor-specific cohorts (non-EWS for the combination of palbociclib with IRN and TMZ) of up to 21 patients each within each combination may also be opened pending observation of antitumor activity observed in the dose finding and dose expansion parts of the study. A Simon's 2-stage optimal design (Table 1) will be used for each of the opened tumor-specific cohorts. Under the null hypothesis of a true response rate that does not exceed 33%, the two-stage design will control one-sided type I error to be approximately 0.10. If the true response rate is at least 58%, type II error will be no more than 0.20. In the first stage, 7 patients will be enrolled in each cohort. Of note, any patients with the specific tumor treated in the dose finding and dose expansion parts of the study will be counted as part of the 7 patients of the first stage of the tumor-specific cohort. If there are 2 confirmed objective responses in these 7 patients, the study will be stopped for ineffectiveness. If there are 6 or more confirmed objective responses in these 7 patients, the study will be stopped for effectiveness. Otherwise, 14 additional patients will be enrolled for a total of 21 in each tumor-specific cohort. The null hypothesis will be rejected if 10 or more confirmed objective responses are observed in 21 patients.

Objective response (OR) is defined as a complete response (CR) or partial response (PR) according to RECIST v. 1.1 or modified RANO for CNS malignancies, and the objective response rate (ORR) is calculated as the percentage of patients with a best overall response of CR or PR. OR is defined as a CR, PR or minor response (MR) according to INRC for neuroblastoma, and the ORR is calculated as the percentage of patients with a best overall response of CR, PR or MR. Confirmation of the response is required. Patients who die, progress, or permanently discontinue study treatment for any reason after being treated prior to documented response will be included in the analysis as non-responders. ORR with confidence intervals will be provided.

Safety analyses will be descriptive in nature. Pooled PK data from Phase 1 and Phase 2 will be reported by predefined age groups.

Study 1 Phase 2

Once the RP2D is confirmed for the combination of palbociclib with IRN and TMZ, the Phase 2 portion of Study 1 will be initiated with the primary objective being to compare the efficacy of palbociclib in combination with IRN and TMZ to IRN and TMZ chemotherapy alone in the treatment of children, adolescents, and young adults with recurrent or refractory EWS. The primary endpoint is event-free survival (EFS) based on investigator assessment. Additional secondary endpoints include OR, PFS, OS, PET-CT response after Cycle 4, safety, PK, QOL and days of hospitalization.

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The primary endpoint of EFS is defined as the time from randomization to first event, where an event includes:

- Progression without achieving a response (CR or PR) or
- Recurrence (following a response) or
- Diagnosis of second malignancy or
- Death without progression or recurrence

Patients last known to be event-free will be censored at the date of the last objective disease assessment that verified lack of disease progression, recurrence or second malignancy.

The sample size for the Phase 2 portion of the study is determined based on the assumptions that median EFS for patients receiving IRN and TMZ chemotherapy alone in the treatment of recurrent and refractory EWS is 4.7 months (McCabe et al, 2020) and an improvement to median EFS of 8.1 months (corresponding to a HR=0.58) for palbociclib in combination with IRN and TMZ is considered clinically significant. A total of approximately 50 EFS events are required in the two treatment arms of the study based on a 2:1 randomization to have at least 80% power to detect a hazard ratio of 0.58 in favor of palbociclib plus IRN and TMZ arm using a 1-sided log-rank test at a significance level of 0.20. Assuming a non-uniform accrual accomplished over a 25-month period and follow-up for about 6 months after the last patient is enrolled, a total sample size of approximately 75 patients (~50 patients in the palbociclib in combination with IRN and TMZ arm and ~25 patients in the IRN and TMZ chemotherapy alone arm) is required. It is anticipated that a minimum of 60% of the patients enrolled in each arm will be pediatric patients (age ≥ 2 and < 18 years old). Randomization will be stratified using block randomization by type and time of current disease recurrence (primary refractory or 1st recurrence < 2 yrs versus 1st recurrence ≥ 2 yrs or 2nd or greater recurrence).

An interim futility analysis will be conducted to allow for early stopping of the study due to futility/no signal of activity based on the primary endpoint of EFS. The analysis will be performed after approximately 30 EFS events (~60% of total events expected) have been documented. If the 1-sided p-value is > 0.4287 ($Z > -0.1796$) at the interim analysis, the Phase 2 portion of the study will be terminated early for lack of efficacy.

The primary analysis of EFS based on investigator assessment will be summarized in the full analysis set using the Kaplan-Meier method and displayed graphically where appropriate. The median EFS and corresponding 2-sided 95% CI will be provided. A stratified log-rank test will be used to compare EFS between the two treatment arms. The hazard ratio and

associated 2-sided 95% CI will be estimated using the stratified Cox proportional hazards model.

Study 3

A Rolling-6 Phase 1 design is used to estimate the MTD, where dose escalations are planned in cohorts of 2 to 6 patients. The MTD, defined as the highest dose level at which 6 patients have been treated with at most 1 patient experiencing a DLT and the next higher dose level has been determined to be too toxic, will be determined separately in less-heavily pre-treated patients (stratum I) and heavily pre-treated patients (stratum II), respectively. Once the MTD has been estimated or the RP2D has been determined, 6 additional patients will be treated at that dose level to better describe the toxicity profile of palbociclib. Adverse event data will be summarized in stratum-specific tables, which will incorporate dose, attribution, and grade information. Any objective responses observed in this trial will be described by dose and by histology.

Study 4

APEC1621I will require a minimum of 20 evaluable patients and a maximum of 49 patients, allowing for 15% inevaluability.

APEC1621I will evaluate a primary cohort of 20 mutation-matched ("biomarker positive") evaluable patients of any histology for the primary study aim of determining the objective response rate (CR/PR) to the agent. Using an A'Hern design with $\alpha=10\%$, a sample of $N=20$ will provide 90% power to detect an improvement in response rate from 5%, if the treatment is ineffective, to 25% if the targeted therapy is sufficiently effective to warrant further study. If there are at least 3 responses out of 20 in the primary cohort, the biomarker/therapy match will be deemed a success.

If ≥ 3 patients in the primary cohort with the same histology show signs of objective response (CR/PR), a histology-specific biomarker positive expansion cohort will open after the primary cohort is completed to up to 7 evaluable patients for a total sample size of 10 evaluable biomarker positive patients with that histology. The Sponsor will open up to 3 such expansion cohorts for biomarker positive patients. Note that this can only happen if the response rate in the primary cohort is at least 45% (9/20), and there cannot be more than 21 additional evaluable patients in total for these expansion cohorts.

Toxicity tables will be constructed to summarize the observed incidence by type of toxicity and grade. Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).

- *Labeling that may result from the study(ies):* You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that palbociclib is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).
- *Format and types of reports to be submitted:* You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should report one of the following designations: Hispanic/Latino or Not Hispanic/Latino.

The studies may also use one of the following additional categories for race, as applicable: Not reported, Multiracial, or Unknown.

The studies may also use one of the following additional categories for ethnicity, as applicable: Not reported or Unknown.

If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the guidance addendum.¹ You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>

document "Study Data Specifications," which is posted on FDA.gov² and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- **Timeframe for submitting reports of the study(ies):** Reports of the above studies must be submitted to the Agency on or before December 5, 2025. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.
- **Response to Written Request:** Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies) but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the FD&C Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and

² <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf>

clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

- (1) the type of response to the Written Request (i.e. complete or partial response);
- (2) the status of the application (i.e. withdrawn after the supplement has been filed or pending);
- (3) the action taken (i.e. approval, complete response); or
- (4) the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.³

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the PHS Act, you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found on the Clinical Trials website.⁴

If you have any questions, contact Maritsa Stephenson, Regulatory Project Manager, at Maritsa.Stephenson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Martha Donoghue, M.D.
Acting Associate Director, Pediatric Oncology
Office of Oncologic Diseases
Center for Drug Evaluation and Research

³ <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm>

⁴ www.ClinicalTrials.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARTHA B DONOGHUE
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