IND 135210
NDA 207103

**WRITTEN REQUEST – AMENDMENT # 1**

Pfizer, Inc.
Attention: Angela Wolford, M.S.
Senior Manager Pfizer Global Regulatory Affairs
445 Eastern Point Road
Groton, CT 06340

Dear Ms. Wolford:

Please refer to your correspondence dated October 7, 2020, requesting changes to FDA's July 3, 2018, Written Request for pediatric studies for palbociclib. We also refer to our December 14, 2020, December 21, 2020, and January 8, 2021 information requests. We acknowledge your December 18, 2020, December 30, 2020, and January 14, 2021, responses formally submitted to IND 135210.

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, remain the same.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter. A clean copy of the Amended Written Request is also included.

Reports of the studies that meet the terms of the Written Request dated July 3, 2018, as amended by this letter 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 new drug application (NDA) / 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- the status of the application (i.e., withdrawn after the supplement has been filed or pending);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, call Maryam Khazraee, Regulatory Project Manager, at 301-796-7119.

Sincerely,

*{See appended electronic signature page}*

Gregory Reaman, MD
Acting Associate Director
Pediatric Oncology
Office of Oncological Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Complete Copy of Written Request as Amended
- Complete Copy of Clean Amended Written Request

[1] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

NDA 207103
~~NDA 212436~~

**AMENDED WRITTEN REQUEST-**
**TRACK CHANGES**

Pfizer, Inc.
Attention: Angela Wolford, M.S.
Senior Manager, Global Regulatory Affairs
445 Eastern Point Road
G~~or~~oton, CT 06340

Dear Ms. Wolford:

Reference is made to your March 6, 2018, revised Proposed Pediatric Study Request for palbociclib. Reference is also made to your amendments submitted on May 25, June 6, June 20, and June 26, 2018, in response to our May 15, June 13, and June 21, 2018, information requests regarding your Proposed Pediatric Study Request.

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 fulvestrant in women 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.

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 ~~increased risk of developing diabetes upon exposure to palbociclib~~.

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 rEECur study, sponsored by 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 a number of chemotherapy regimens, with the goal of identifying the optimum chemotherapy regimen based on the balance between efficacy and toxicity. It is anticipated that palbociclib will be added to one of the remaining chemotherapy arms in a future amendment to the rEECur study (Study 2, referred to below).

Results from the second interim assessment of the rEECur Study demonstrated that the irinotecan (IRN) and temozolomide (TMZ) chemotherapy combination is less effective than the topotecan (TOPO) and cyclophosphamide (CTX) combination or single-agent ifosfamide chemotherapy (McCabe et al, 2020). As a result, the rEECur Study DMC recommended to discontinue further enrollment to the IRN/TMZ chemotherapy arm from the rEECur study. In addition, the EEC 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 (PFS and OS) within the rEECur trial to date, the EEC has proposed PFS as the primary endpoint of Phase 2 of ~~Study 2~~rEECur. PFS is defined as the time from randomization until first event (progression, recurrence following response or death without progression or recurrence). EFS is defined as the time from randomization until first event (progression, recurrence following response, second malignancy or death without progression or recurrence). Given the minimal rate of second malignancies in

the studied patient population, the EEC further decided to use EFS, as the primary endpoint for Phase 2 of ~~Study 2~~ rEECur. ORR, PFS and OS will continue to be assessed as the secondary efficacy endpoints.

The rationale for the changes to Study 1 are based on the results above from the IRN and TMZ arm, and the pooled efficacy data across all ~~TOPO and CTX~~ arms from ~~Study 2~~the rEECur study.

- *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)**: An open-label, dose-escalation/determination and cohort expansion study to evaluate the safety, pharmacokinetics (PK) and antitumor activity of palbociclib in combination with temozolomide (TMZ) and irinotecan (IRN) and palbociclib in combination with topotecan (TOPO) and cyclophosphamide (CTX) in patients with relapsed or refractory solid tumors. The dose-escalation/determination portion 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 ~~at the MTD or~~ 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~~. (Study A5481092)~~. Of note, although patients with EWS can enroll into the dose ~~escalation~~determination part and the~~or~~ dose expansion ~~part~~ cohort of the study for palbociclib in combination with TOPO and CTX, a tumor specific cohort for EWS will not be opened in Study 1 as Study 2 will enroll ~~only~~ patients with EWS to evaluate efficacy of palbociclib in combination with TOPO and CTX. Also, regardless of the responses observed in the dose escalation and dose expansion cohorts, an EWS tumor specific cohort will be opened for palbociclib in combination with IRN and TMZ.
~~Once a~~
This EWS tumor specific cohort will follow the~~is opened, a~~ Simon's 2-stage minimax design ~~will be followed~~ with the decision rules as shown below. Under the null hypothesis of a true ORR that does not exceed 20%, the 2-stage minimax design will control 1-sided type I error to be approximately 0.10 and has power of 80% when the true ORR is 40% (Table 1).

**Table 1. Simon's 2-Stage Minimax Design Decision Rules for EWS Tumor-Specific Cohort**

| | **Cumulative Number of Responses[a]** | **Decision** |
|---|---|---|
| **Stage 1: Enroll a total of 14 patients** | 2 or less | Terminate enrollment - agent ineffective |
| | 3 or more | Proceed to Stage 2 |
| **Stage 2: Enroll 10 additional patients** | 7 or less | Agent ineffective |
| | 8 or more | Agent effective |

a. Assumption based on an objective response rate of 20% for IRN+TMZ and 40% for palbociclib+IRN+TMZ, respectively.

If other 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 2).

**Table 2. 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] ~~or more~~ | Terminate enrollment-agent effective |
| **Stage 2: Enroll 14 additional patients (N=21 total)** | 9 or less | Agent ineffective |
| | 10 or more | Agent effective |

a. Assumption based on an objective response rate of ~~-~~33% for ~~vs 58% for ORR~~ IRN/TMZ or TOPO/CTX and 58% for ~~vs~~ 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 ~~parts~~ cohort of the study.
c. Lower bound of the Wilson's 2-sided ~~95~~80% CI is greater than ~~58~~62%

An initial Clinical Study Report (CSR) will be generated for Study 1 following the completion of the dose finding and initial 12 patient dose expansion part for each combination of the study in order to align with Pfizer's agreed upon European Paediatric Investigation Plan.

A supplemental CSR for Study 1 will be generated containing ~~additional~~ safety and efficacy data ~~(~~from the any tumor-specific cohort(s) from the data cutoff for the initial CSR until the data cutoff date that meets the FDA submission requirement for completed **Studies 2** and **3**. The initial CSR and supplemental CSR from **Study 1** will be submitted along with the final CSRs from **Study 2** and **Study 3** (and information from

**Study 4**, if available, as described below) to satisfy the requirements of the Written Request. If no additional tumor-specific cohorts are opened, then the supplemental CSR for **Study 1** with the palbociclib+IRN+TMZ EWS tumor-specific cohort data could be considered the final CSR. Likewise, if all data from any tumor-specific cohorts are available by the submission timeline, the supplemental CSR will be considered the final CSR.

~~If any tumor-specific cohorts are still ongoing at the time of data cutoff for the FDA submissionOf note, a final CSR, including any new safety and efficacy data from patients in the remaining tumor-specific cohorts will be generated at the end of the study. If needed, this final CSR will be submitted as soon as it is available and not considered a requirement for Written Request since thet~~The potential duration of the tumor-specific cohorts, especially in these rare pediatric settings, may take an extended time to enroll and complete. ~~and submitted to the FDA within the time period outlined in the Written Request.~~ If accrual to the disease specific cohorts of Study 1 is less than anticipated, sponsor may request an amendment to the Written Request.

**Study 2***:* A randomized, open-label, activity-estimating trial, comparing treatment arms of ~~TMZ~~ TOPO and ~~IRN~~ CTX alone with the combination of palbociclib plus ~~TMZ~~ TOPO and ~~IRN~~CTX, in the treatment of patients with recurrent and/or refractory EWS (rEECur Study, conducted by the EURO EWING Consortium).

**Study 3**: An ~~ongoing,~~ 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 1-3, 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 1-3. The Written Request may be amended upon request from Pfizer to either remove the Study 4 WR obligation or delay data submission in the event that results from Study 4 are not available for submission when Studies 1-3 are completed for submission.

Efficacy in pediatric patients ages ≥~~4~~ 2 to <18 years with recurrent or refractory EWS in **Study 2** will be supported by data in adult patients ~~<50 years of age~~ 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. ~~As there are no known differences in the biology of EWS across age ranges, the eligibility criterion in the rEECur study protocol includes patients <50 years of age.~~ A minimum of

25~~% of~~ patients per arm for the palbociclib in combination with TOPO+CTX arm and the TOPO+CTX alone arm enrolled in Study 2 must be <18~~17~~ years of age.

The confirmation ~~estimation~~ of the recommended phase 2 dose~~maximum tolerated dose (MTD)/~~(RP2D) from ~~the dose escalation part of~~**Study 1** must be completed before initiating the palbociclib and ~~TMZ/IRN~~TOPO+CTX arm of **Study 2**.

- *Objective of each study:*

**Study 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 (EWS and Other Tumor Types):
- To evaluate the safety and confirm the RP2D for the combination of palbociclib+TMZ+IRN and the combination of palbociclib+TOPO+CTX ~~at the RP2D~~ 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.

**Study 2**
- To compare the efficacy of palbociclib in combination with TOPO and CTX to TOPO and CTX chemotherapy alone in the treatment of patients with recurrent and refractory EWS

- ~~To determine ORR in pediatric patients with recurrent/refractory EWS treated with palbociclib plus TMZ and IRN combination treatment arm compared to treatment with TMZ and IRN.~~
- To ~~confirm~~ evaluate toxicity, and safety of palbociclib plus ~~TMZ~~ TOPO and ~~IRN~~ CTX in patients with recurrent and refractory EWS~~pediatric patients~~.
- To evaluate the PK of palbociclib, TOPO, and CTX in patients with recurrent or refractory EWS
- To assess the impact of the combination of palbociclib with TOPO and CTX treatment on the quality of life (QoL) of patients with refractory and recurrent 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

Dose Escalation Part (palbociclib in combination with IRN and TMZ): A minimum of 6 patients to a maximum of 24~~12~~ 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.

EWS tumor specific cohort (palbociclib in combination with IRN and TMZ): A minimum of 14 to a maximum of 24 patients with recurrent or refractory EWS tumor.

**Study 2**
A minimum of 25 pediatric patients age ≥42 to <18 ~~4 years and ≤18~~ years per arm (palbociclib+~~TMZ~~TOPO+~~IRN~~ CTX and ~~TMZ~~TOPO+~~IRN~~CTX alone) with recurrent and/or refractory EWS.

Given the rarity of EWS, additional adult patients may be included to provide for a more robust analysis.

**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. Limited PK sample collections of palbociclib will be included in **Study 2**, which will contribute to a pooled POP-PK analysis using pooled data from **Studies 1**, **2**, 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~~ 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**
**Dose Escalation/Dose Determination Parts:**

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

**Dose Expansion Parts and Tumor-Specific Cohorts (EWS and Other Tumor Types):**

- 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
- ~~will be o~~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.
- ~~Important~~ Secondary endpoints will include:
  - Duration of Response (DOR), ~~Oobjective Response (OR),~~ PFS, and Overall Survival (OS).
  - ~~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; and~~
  - PK parameters of palbociclib, TMZ, ~~and~~ IRN, TOPO, and CTX: multiple dose $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit.

**Study 2**

- The primary endpoint is event free survival (EFS). ~~ORR by CT or MRI after Cycle 4; response measured using the RECIST version 1.1 c~~
  The key secondary endpoints are:~~event free survival (EFS), PFS and OS;~~
  - ~~toxicity, defined by CTCAE version 4.0;~~Toxicity defined by National Cancer Institute [NCI] Common Terminology Criteria for Adverse events [CTCAE] version 4.0
  - Objective Response (OR)~~R~~ by CT or MRI after Cycle 2, Cycle 4, Cycle 6 and at the end of trial treatment; response measured using the RECIST version 1.1 criteria.
  - PFS
  - OS
  - PET-CT response after Cycle 4, compared to objective response on ~~standard~~ MRI/CT;
  - QoL at baseline and after Cycles 2 and 4 using age-appropriate tools;
  - D~~d~~ays spent in hospital; and
  - PK concentrations ~~parameters~~ of palbociclib, TOPO~~TMZ~~, and CTX~~IRN~~

**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,
  - ~~I~~individual PK parameters of palbociclib~~, and~~
    - ~~population PK parameters.~~

**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. Reproductive effects will be monitored by study sites per their respective local standards. 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 Studies 1 and 2, 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 of lumbar spine, 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. Dental abnormalities/tooth discoloration will be assessed by the care provider 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. 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 be recommended.

The most common adverse reactions (incidence ≥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) (≥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 (≥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 ~~and nausea~~ (24.3% ~~each~~), 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, ~~and~~ 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/m$^2$, 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/m$^2$ on Days 1 to 5 and IRN administered intravenously (IV) at 50 mg/m$^2$ 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/m$^2$ or escalated up to 115~~75~~ mg/m$^2$.

**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/m$^2$ 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/m$^2$.

Palbociclib will be administered with TOPO at 0.75 mg/m$^2$ IV over 30 minutes ~~(±10%)~~ and CTX at 250 mg/m$^2$ IV over 30-60 minutes ~~(±10%)~~ on Days 1-5 of each 21-day cycle.

**Study 1 (dose expansion and Ewing Sarcoma and other tumor-specific cohorts) palbociclib+IRN+TMZ ~~(for Ewing Sarcoma patients)~~:**

Palbociclib will be administered daily for 14 days followed by 7 days off in 3-week cycles. The ~~calculated~~ starting dose level in dose expansion will be ~~determined based on the~~ 75 mg/m$^2$ ~~MTD~~ which has been determined as the MTD for palbociclib in combination with IRN+TMZ in ~~from~~ the dose escalation part of Study 1. The dose level in Ewing Sarcoma and other 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, ~~140 mg, 180 mg, and 250 mg~~ capsules of TMZ will be used to generate the treatment dose of 100 mg/m$^2$ 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/m$^2$ 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/m$^2$ IV over 30 minutes (±10%) on Days 1-5 of each 21-day cycle.

CTX will be dosed at 250 mg/m$^2$ 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/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 2**

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 from Study 1.

~~On the basis of the calculated BSA, 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 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.~~

The doses of TOPO and CTX will be 0.75 mg/m$^2$ daily on Days 1-5 and 250 mg/m$^2$ daily on Days 1-5, respectively. All dosing will be in 21-day cycles. Subcutaneous daily G-CSF (5 µg/kg/dose daily) will be mandatory starting 24-48 hours after final TOPO+CTX infusion (Day 6/Day 7 of each cycle). The G-CSF must be stopped 24 hours prior to the next treatment cycle. 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 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/m$^2$. Depending on the safety evaluation of the initial cohort, palbociclib may be escalated to 75 mg/m$^2$ or escalated up to 95 mg/m$^2$.

**Study 4**

Palbociclib is taken orally once daily at 75 mg/m$^2$ 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**

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 ~~and at least 33% of patients experience a DLT at the next higher dose~~.

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/m$^2$). 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/m$^2$. 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~~s~~ been determined, the respective Dose Expansion ~~Part~~ 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.~~;~~

Once the RP2D is confirmed for palbociclib+IRN+TMZ following the dose expansion, the combination will be evaluated in a cohort of patients with EWS (maximum of 24 patients), regardless of the responses observed in dose escalation part and/or dose expansion cohort, to determine the antitumor activity in this specific tumor type following a Simon's 2-stage minimax design (Table 1). The null hypothesis that the true objective response rate (ORR) is 20% will be tested against a 1-sided alternative hypothesis of 40%, where the 20% ORR under the null hypothesis was based on the results of the second interim analysis of rEECur in 118 patients with EWS who received IRN and TMZ. In the first stage, 14 patients will be accrued. If there are 2 or fewer confirmed objective responses in these 14 patients, the study will be stopped for lack of activity. Otherwise, 10 additional patients will be accrued for a total of 24 patients. The null hypothesis will be rejected if 8 or more confirmed objective responses are observed in the total of 24 patients. This design yields a type I error rate of approximately 10% and power of 80% when the true ORR is 40%.

Other tumor-specific cohorts (non-EWS) of up to 21 patients each within each combination may also be ~~enrolled~~ 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 2) 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 ~~no more than~~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 ~~and 95%~~with confidence intervals will be provided.

Safety analyses will be descriptive in nature. PK data in the Dose Escalation Part and Dose Expansion ~~Part~~ Cohort will be reported by predefined age groups.

**Study 2**

~~Assuming the ORR for TMZ+IRN treatment is 55%, the palbociclib+TMZ+IRN and TMZ+IRN portion of the rEECur study will have at least 80% power to detect a minimum 27% improvement of ORR using one-sided significance level of 0.1 if a minimum of 25 pediatric patients with recurrent and/or refractory EWS per arm are randomized between the palbociclib+TMZ+IRN and TMZ+IRN treatment arms in a 1:1 ratio. Since adult patients may also be enrolled into the study, the exact final number of total patients for both treatment arms will be higher. Efficacy analyses are planned after a minimum of 25 pediatric patients in both the palbociclib +TMZ+IRN and TMZ+IRN treatment arms have been recruited and assessed for the primary study outcome. The primary analysis will be descriptive. For each treatment arm, the number of responders (and proportion with confidence intervals) will be presented. Tumor response will be assessed using RECIST version 1.1.~~The primary objective of this study is to compare the efficacy of palbociclib in combination with TOPO and CTX to TOPO and CTX chemotherapy alone in prolonging EFS in the treatment of patients with recurrent and refractory EWS. All primary and secondary endpoints based on radiological assessments of tumor burden (i.e. EFS, PFS, and OR) will be derived using the local radiologist's/investigator's assessment. OS, QOL, and safety will also be considered as secondary endpoints.

The primary endpoint of event-free survival (EFS) is defined as the time from randomization to first event, where an event is:

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

For those patients who do not experience an event during the course of the trial, EFS times will be censored at the date of their last available trial assessment.

The sample size for this study is determined based on the assumptions that 1-year EFS rate for patients receiving TOPO and CTX chemotherapy alone in the treatment of patients with recurrent and refractory EWS is 25% and a risk reduction by ~34% (a hazard ratio of 0.66) or an improvement by 15% to 1-year EFS rate of 40% in palbociclib in combination with TOPO and CTX is clinically significant. Approximately of 70 events are required in the two arms of the study based on a 1:1 randomization to have 80% power to detect a hazard ratio of 0.66 in favor of the palbociclib in combination with TOPO and CTX arm using a 1-sided significance level of 0.20. It is understood that this 1-sided significance level of 0.20 may not support registration. A non-uniform accrual accomplished over a 20-month period and follow-up for about 6 months after the last patient is enrolled, a total sample size of approximately 102 patients (~51 in the palbociclib in combination with TOPO and CTX arm and ~51 in the TOPO and CTX chemotherapy alone arm) is required. Approximately 50% of these 102 patients will be pediatric patients.

An interim futility analysis to stop the study early for futility/no signal of activity is planned after the first 25 patients per arm have been recruited. If the 1-sided p-value is > 0.50 at the interim analysis, the palbociclib in combination with TOPO and CTX arm will be stopped.

The primary analysis of EFS based on the assessment of investigator will be summarized in the ITT population (approximately 50% of those patients being pediatric patients) using the Kaplan-Meier method and displayed graphically where appropriate. The median EFS time and corresponding 2-sided 95% CI for the median will be provided. EFS estimates at 1, 2, and 5-years (if appropriate) with CI will be reported. A stratified log-rank test will be used for testing the hypothesis. The hazard ratio~~,~~ and its 95% CI ~~and p-value~~ adjusted for the stratification factor~~s~~ will be estimated using Cox proportional hazards model. Proportional hazards assumption will be assessed.

**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 4 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 in the study(ies) 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 use one of

the following designations: Hispanic/Latino or Not Hispanic/Latino. 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.gov[2] 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 ~~31~~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.

[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

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 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

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

results. Additional information on submission of such information can be found on the Clinical Trials website.[4]

If you have any questions, call Maryam Khazraee, Regulatory Health Project Manager, at 301-796-7119.

Sincerely,

*{See appended electronic signature page}*

Gregory Reaman, M.D.
Associate Director, Pediatric Oncology
Office of Oncologic Diseases
Center for Drug Evaluation and Research

[4] www.ClinicalTrials.gov

IND 135210
NDA 207103

**AMENDED WRITTEN REQUEST-CLEAN COPY**

Pfizer, Inc.
Attention: Angela Wolford, M.S.
Senior Manager, Global Regulatory Affairs
445 Eastern Point Road
Groton, CT 06340

Dear Ms. Wolford:

Reference is made to your March 6, 2018, revised Proposed Pediatric Study Request for palbociclib. Reference is also made to your amendments submitted on May 25, June 6, June 20, and June 26, 2018, in response to our May 15, June 13, and June 21, 2018, information requests regarding your Proposed Pediatric Study Request.

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 fulvestrant in women 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.

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 rEECur study, sponsored by 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 a number of chemotherapy regimens, with the goal of identifying the optimum chemotherapy regimen based on the balance between efficacy and toxicity. It is anticipated that palbociclib will be added to one of the remaining chemotherapy arms in a future amendment to the rEECur study (Study 2, referred to below).

Results from the second interim assessment of the rEECur Study demonstrated that the irinotecan (IRN) and temozolomide (TMZ) chemotherapy combination is less effective than the topotecan (TOPO) and cyclophosphamide (CTX) combination or single-agent ifosfamide chemotherapy (McCabe et al, 2020). As a result, the rEECur Study DMC recommended to discontinue further enrollment to the IRN/TMZ chemotherapy arm from the rEECur study. In addition, the EEC 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 (PFS and OS) within the rEECur trial to date, the EEC has proposed PFS as the primary endpoint of Phase 2 of rEECur. PFS is defined as the time from randomization until first event (progression, recurrence following response or death without progression or recurrence). EFS is defined as the time from randomization until first event (progression, recurrence following response, second malignancy or death without progression or recurrence). Given the minimal rate of second malignancies in the studied patient population, the EEC further decided to use EFS, as the primary endpoint for Phase 2 of rEECur. ORR, PFS and OS will continue to be assessed as the secondary efficacy endpoints.

The rationale for the changes to Study 1 are based on the results above from the IRN and TMZ arm, and the pooled efficacy data across all arms from the rEECur study.

- *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)**: An open-label, dose-escalation/determination and cohort expansion study to evaluate the safety, pharmacokinetics (PK) and antitumor activity of palbociclib in combination with temozolomide (TMZ) and irinotecan (IRN) and palbociclib in combination with topotecan (TOPO) and cyclophosphamide (CTX) in patients with relapsed or refractory solid tumors. The dose-escalation/determination portion 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. Of note, although patients with EWS can enroll into the dose determination part and the dose expansion cohort of the study for palbociclib in combination with TOPO and CTX, a tumor specific cohort for EWS will not be opened in Study 1 as Study 2 will enroll patients with EWS to evaluate efficacy of palbociclib in combination with TOPO and CTX. Also, regardless of the responses observed in the dose escalation and dose expansion cohorts, an EWS tumor specific cohort will be opened for palbociclib in combination with IRN and TMZ.

This EWS tumor specific cohort will follow the Simon's 2-stage minimax design with the decision rules as shown below. Under the null hypothesis of a true ORR that does not exceed 20%, the 2-stage minimax design will control 1-sided type I error to be approximately 0.10 and has power of 80% when the true ORR is 40% (Table 1).

**Table 1. Simon's 2-Stage Minimax Design Decision Rules for EWS Tumor-Specific Cohort**

| | Cumulative Number of Responses[a] | Decision |
|---|---|---|
| **Stage 1:** | 2 or less | Terminate enrollment - agent ineffective |
| **Enroll a total of 14 patients** | 3 or more | Proceed to Stage 2 |
| **Stage 2:** | 7 or less | Agent ineffective |
| **Enroll 10 additional patients** | 8 or more | Agent effective |

a. Assumption based on an objective response rate of 20% for IRN+TMZ and 40% for palbociclib+IRN+TMZ, respectively.

If other 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 2).

**Table 2. 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 |

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%

An initial Clinical Study Report (CSR) will be generated for Study 1 following the completion of the dose finding and initial 12 patient dose expansion part for each combination of the study in order to align with Pfizer's agreed upon European Paediatric Investigation Plan.

A supplemental CSR for Study 1 will be generated containing safety and efficacy data from any tumor-specific cohort(s) from the data cutoff for the initial CSR until the data cutoff date that meets the FDA submission requirement for completed **Studies 2** and **3**. The initial CSR and supplemental CSR from **Study 1** will be submitted along with the final CSRs from **Study 2** and **Study 3** (and information from **Study 4**, if available, as described below) to satisfy the requirements of the Written Request. If no additional tumor-specific cohorts are opened, then the supplemental CSR for **Study 1** with the palbociclib+IRN+TMZ EWS tumor-specific cohort data could be considered the final CSR.

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 2***:* A randomized, open-label, activity-estimating trial, comparing treatment arms of TOPO and CTX alone with the combination of palbociclib plus TOPO and CTX, in the treatment of patients with recurrent and/or refractory EWS (rEECur Study, conducted by the EURO EWING Consortium).

**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 1-3, 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 1-3. The Written Request may be amended upon request from Pfizer to either remove the Study 4 WR obligation or delay data submission in the event that results from Study 4 are not available for submission when Studies 1-3 are completed for submission.

Efficacy in pediatric patients ages ≥2 to <18 years with recurrent or refractory EWS in **Study 2** will be supported by data in adult patients 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 25 patients per arm for the palbociclib in combination with TOPO+CTX arm and the TOPO+CTX alone arm enrolled in Study 2 must be <18 years of age.

The confirmation of the recommended phase 2 dose (RP2D) from **Study 1** must be completed before initiating the palbociclib and TOPO+CTX arm of **Study 2**.

- *Objective of each study:*

**Study 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 (EWS and Other Tumor Types):
- 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.

**Study 2**
- To compare the efficacy of palbociclib in combination with TOPO and CTX to TOPO and CTX chemotherapy alone in the treatment of patients with recurrent and refractory EWS
- To evaluate toxicity, and safety of palbociclib plus TOPO and CTX in patients with recurrent and refractory EWS.
- To evaluate the PK of palbociclib, TOPO, and CTX in patients with recurrent or refractory EWS
- To assess the impact of the combination of palbociclib with TOPO and CTX treatment on the quality of life (QoL) of patients with refractory and recurrent 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

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.

EWS tumor specific cohort (palbociclib in combination with IRN and TMZ): A minimum of 14 to a maximum of 24 patients with recurrent or refractory EWS tumor.

**Study 2**
A minimum of 25 pediatric patients age ≥2 to <18 years per arm (palbociclib+TOPO+CTX and TOPO+CTX alone) with recurrent and/or refractory EWS.

Given the rarity of EWS, additional adult patients may be included to provide for a more robust analysis.

**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. Limited PK sample collections of palbociclib will be included in **Study 2**, which will contribute to a pooled POP-PK analysis using pooled data from **Studies 1**, **2**, 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**
**Dose Escalation/Dose Determination Parts:**
- The primary endpoint will be first-cycle dose-limiting toxicities (DLTs).

**Dose Expansion Parts and Tumor-Specific Cohorts (EWS and Other Tumor Types):**
- 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.

**Study 2**

- The primary endpoint is event free survival (EFS).
  The key secondary endpoints are:
  - Toxicity defined by National Cancer Institute [NCI] Common Terminology Criteria for Adverse events [CTCAE] version 4.0
  - Objective Response (OR) by CT or MRI after Cycle 2, Cycle 4, Cycle 6 and at the end of trial treatment; response measured using the RECIST version 1.1 criteria.
  - PFS
  - OS
  - PET-CT response after Cycle 4, compared to objective response on MRI/CT;
  - QoL at baseline and after Cycles 2 and 4 using age-appropriate tools;
  - Days spent in hospital; and
  - PK concentrations of palbociclib, TOPO, and CTX

**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. Reproductive effects will be monitored by study sites per their respective local standards. 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 Studies 1 and 2, 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 of lumbar spine, 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. Dental abnormalities/tooth discoloration will be assessed by the care provider 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. 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 be recommended.

The most common adverse reactions (incidence ≥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) (≥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 (≥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/m$^2$, 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/m$^2$ on Days 1 to 5 and IRN administered intravenously (IV) at 50 mg/m$^2$ 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/m$^2$ or escalated up to 115 mg/m$^2$.

**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/m$^2$ 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/m$^2$.

Palbociclib will be administered with TOPO at 0.75 mg/m$^2$ IV over 30 minutes and CTX at 250 mg/m$^2$ IV over 30-60 minutes on Days 1-5 of each 21-day cycle.

**Study 1 (dose expansion and Ewing Sarcoma and other 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/m$^2$ 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 Ewing Sarcoma and other 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/m$^2$ 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/m$^2$ 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/m$^2$ IV over 30 minutes (±10%) on Days 1-5 of each 21-day cycle.

CTX will be dosed at 250 mg/m$^2$ 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/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 2**

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 from Study 1.

The doses of TOPO and CTX will be 0.75 mg/m$^2$ daily on Days 1-5 and 250 mg/m$^2$ daily on Days 1-5, respectively. All dosing will be in 21-day cycles. Subcutaneous daily G-CSF (5 µg/kg/dose daily) will be mandatory starting 24-48 hours after final TOPO+CTX infusion (Day 6/Day 7 of each cycle). The G-CSF must be stopped 24 hours prior to the next treatment cycle. 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 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/m$^2$. Depending on the safety evaluation of the initial cohort, palbociclib may be escalated to 75 mg/m$^2$ or escalated up to 95 mg/m$^2$.

**Study 4**

Palbociclib is taken orally once daily at 75 mg/m$^2$ 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**

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/m$^2$). 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/m$^2$. 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.

Once the RP2D is confirmed for palbociclib+IRN+TMZ following the dose expansion, the combination will be evaluated in a cohort of patients with EWS (maximum of 24 patients), regardless of the responses observed in dose escalation part and/or dose expansion cohort, to determine the antitumor activity in this specific tumor type following a Simon's 2-stage minimax design (Table 1). The null hypothesis that the true objective response rate (ORR) is 20% will be tested against a 1-sided alternative hypothesis of 40%, where the 20% ORR under the null hypothesis was based on the results of the second interim analysis of rEECur in 118 patients with EWS who received IRN and TMZ. In the first stage, 14 patients will be accrued. If there are 2 or fewer confirmed objective responses in these 14 patients, the study will be stopped for lack of activity. Otherwise, 10 additional patients will be accrued for a total of 24 patients. The null hypothesis will be rejected if 8 or more confirmed objective responses are observed in the total of 24 patients. This design yields a type I error rate of approximately 10% and power of 80% when the true ORR is 40%.

Other tumor-specific cohorts (non-EWS) 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 2) 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. PK data in the Dose Escalation Part and Dose Expansion Cohort will be reported by predefined age groups.

**Study 2**

The primary objective of this study is to compare the efficacy of palbociclib in combination with TOPO and CTX to TOPO and CTX chemotherapy alone in prolonging EFS in the treatment of patients with recurrent and refractory EWS. All primary and secondary endpoints based on radiological assessments of tumor burden (i.e. EFS, PFS, and OR) will be derived using the local radiologist's/investigator's assessment. OS, QOL, and safety will also be considered as secondary endpoints.

The primary endpoint of event-free survival (EFS) is defined as the time from randomization to first event, where an event is:

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

For those patients who do not experience an event during the course of the trial, EFS times will be censored at the date of their last available trial assessment.

The sample size for this study is determined based on the assumptions that 1-year EFS rate for patients receiving TOPO and CTX chemotherapy alone in the treatment of patients with recurrent and refractory EWS is 25% and a risk reduction by ~34% (a hazard ratio of 0.66) or an improvement by 15% to 1-year

EFS rate of 40% in palbociclib in combination with TOPO and CTX is clinically significant. Approximately of 70 events are required in the two arms of the study based on a 1:1 randomization to have 80% power to detect a hazard ratio of 0.66 in favor of the palbociclib in combination with TOPO and CTX arm using a 1-sided significance level of 0.20. It is understood that this 1-sided significance level of 0.20 may not support registration. A non-uniform accrual accomplished over a 20-month period and follow-up for about 6 months after the last patient is enrolled, a total sample size of approximately 102 patients (~51 in the palbociclib in combination with TOPO and CTX arm and ~51 in the TOPO and CTX chemotherapy alone arm) is required. Approximately 50% of these 102 patients will be pediatric patients.

An interim futility analysis to stop the study early for futility/no signal of activity is planned after the first 25 patients per arm have been recruited. If the 1-sided p-value is > 0.50 at the interim analysis, the palbociclib in combination with TOPO and CTX arm will be stopped.

The primary analysis of EFS based on the assessment of investigator will be summarized in the ITT population (approximately 50% of those patients being pediatric patients) using the Kaplan-Meier method and displayed graphically where appropriate. The median EFS time and corresponding 2-sided 95% CI for the median will be provided. EFS estimates at 1, 2, and 5-years (if appropriate) with CI will be reported. A stratified log-rank test will be used for testing the hypothesis. The hazard ratio and its 95% CI adjusted for the stratification factor will be estimated using Cox proportional hazards model. Proportional hazards assumption will be assessed.

**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 4 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 in the study(ies) 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 use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. 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.gov[2] 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.

[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

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 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, call Maryam Khazraee, Regulatory Health Project Manager, at 301-796-7119.

Sincerely,

*{See appended electronic signature page}*

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm
[4] www.ClinicalTrials.gov

Gregory Reaman, M.D.
Associate Director, Pediatric Oncology
Office of Oncologic Diseases
Center for Drug Evaluation and Research

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**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.**

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/s/

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