



NDA 207103

WRITTEN REQUEST

Pfizer Inc.
Attention: Michelle Y. Kite
Director, Worldwide Safety and Regulatory
10646 Science Drive Center
San Diego, CA 92121

Dear Ms. Kite:

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 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.

- *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: An open-label, dose-escalation and cohort expansion study to evaluate the safety, pharmacokinetics (PK) and antitumor activity of palbociclib in combination with temozolomide (TMZ) and irinotecan (IRN). The dose escalation portion will include pediatric patients with recurrent or refractory solid tumors. The dose expansion portion will first enroll and treat a minimum of 12 patients with any recurrent or refractory solid tumor type at the MTD or recommended Phase 2 dose (RP2D). If 2 or more patients from the dose escalation or dose expansion 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 within the specific cancer subtype. (Study A5481092). Of note, although patients with EWS can enroll into the dose escalation or dose expansion part of the study, a tumor specific cohort for EWS will not be opened in Study 1 as Study 2 will enroll only patients with EWS.

Once a tumor specific cohort is opened, a Simon 2-stage design will be followed with the decision rules as shown below:

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

^aAssumption 33% vs 58% for ORR IRN/TMZ vs palbo/IRN/TMZ, respectively

^bEvaluated patients will include the 2 objective responses observed and any other patients with the same tumor type during the dose escalation and dose expansion parts of the study^cLower bound of 2-sided 95% CI is greater than 58%

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 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 tumor-specific cohorts) 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.

Of note, a final CSR, including any new safety and efficacy data from patients in the tumor-specific cohorts will be generated 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 and IRN with palbociclib plus TMZ and IRN, 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 to < 18 years with recurrent or refractory EWS in **Study 2** will be supported by data in 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 enrolled in Study 2 must be < 17 years of age.

The estimation of the maximum tolerated dose (MTD)/RP2D from the dose-escalation part of **Study 1** must be completed before initiating the palbociclib and TMZ/IRN 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 anti-tumor activity of palbociclib combined with TMZ and IRN

Dose Expansion Part:

- To evaluate the safety and confirm the RP2D for the combination of palbociclib+TMZ+IRN 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 anti-tumor activity of palbociclib combined with TMZ and IRN 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 in children, adolescents and young adults with recurrent or refractory solid tumors when given in combination.

Study 2

- 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 toxicity, and safety of palbociclib plus TMZ and IRN in pediatric patients.

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: A minimum of 4 patients to a maximum of 12 patients with recurrent or refractory solid tumors

Dose Expansion Part: A minimum of 12 patients 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.

Study 2

A minimum of 25 pediatric patients age ≥ 4 years and ≤ 18 years per arm (palbociclib+TMZ+IRN and TMZ+IRN) 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.

A minimum of 6 patients treated with the combination of palbociclib+TMZ+IRN 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 minimum 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 Part:

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

Dose Expansion Part:

- The primary endpoint will be objective tumor response as assessed using Response Evaluation Criteria in Solid Tumor (RECIST version 1.1) or modified Revised Assessment in Neuro Oncology (RANO) for CNS malignancies.
- Important secondary endpoints will include:
 - Duration of Response (DOR), Objective 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 $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $C_{ss,trough}$, and CL/F, as data permit.

Study 2

- The primary endpoint is ORR by CT or MRI after Cycle 4; response measured using the RECIST version 1.1 criteria.
The key secondary endpoints are:
 - event-free survival (EFS), PFS and OS;
 - toxicity, defined by CTCAE version 4.0;
 - ORR by CT or MRI after Cycle 2, Cycle 6 and at the end of trial treatment;
 - PET-CT response after Cycle 4, compared to standard MRI/CT;
 - QoL at baseline and after Cycles 2 and 4 using age-appropriate tools;
 - days spent in hospital; and
 - PK parameters of palbociclib, TMZ, and 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,
 - 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 in 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 $\geq 10\%$) occurring in studies supporting approval of palbociclib for use in combination with other agents in patients with advanced or metastatic breast cancer were neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, anemia, alopecia, diarrhea, thrombocytopenia, rash, vomiting, decreased appetite, asthenia, and pyrexia.

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

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 will be administered based on body surface area (BSA) dosing. BSA will be calculated by individual investigative site standard methods.

Study 1 (dose escalation):

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

minutes. Depending on the safety evaluation of the initial cohort, palbociclib may be de-escalated to 40 mg/m² or escalated up to 75 mg/m².

Study 1 (dose expansion):

Palbociclib will be administered daily for 14 days followed by 7 days off in 3-week cycles. The calculated dose will be determined based on the MTD from the dose escalation part of 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.

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.

Study 3

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

Study 4

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

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

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

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

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

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

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

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

Study 1

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 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. Once the MTD has been determined, the Dose Expansion Part will enroll a minimum of 12 patients with any solid tumor type to further evaluate the safety and obtain preliminary assessment of antitumor activity in this patient population; tumor-specific cohorts of up to 21 patients each may also be enrolled pending observation of antitumor activity observed in the dose finding and dose expansion parts of the study. A Simon's 2 stage design 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 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 objective responses in these 7 patients, the study will be stopped for ineffectiveness. If there are 6 or more 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 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 RANO for CNS malignancies. Confirmation of the response is required. The objective response rate (ORR) is defined as the percentage of patients with a CR or PR. 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% confidence interval will be provided.

Safety analyses will be descriptive in nature. PK data in the Dose Escalation Part and Dose Expansion Part 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.

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. 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 the <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf> and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf>.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before December 31, 2025. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.
- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

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

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

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

In accordance with section 505A(k)(1) of the 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 at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872>.

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 Public Health Service Act (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 at www.ClinicalTrials.gov.

If you have any questions, call Missiratch (Mimi) Biable, M.S., R.A.C (US), Lead Regulatory Helath Project Manager, at 301-796-0154.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, M.D.
Associate Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

GREGORY H REAMAN
07/03/2018