



FDA Briefing Document

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)

June 22, 2017

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office.

We have brought the following issues to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee.

Information will be presented to gauge investigator interest in exploring potential pediatric development plans for three products in various stages of development for adult cancer indications. The subcommittee will consider and discuss issues concerning diseases to be studied, patient populations to be included, and possible study designs in the development of these products for pediatric use. The discussion will also provide information to the Agency pertinent to the formulation of Written Requests for pediatric studies, if appropriate. The products under consideration are: (1) Olaratumab, application sponsored by Eli Lilly and Company and (2) Prexasertib, application sponsored by Eli Lilly and Company.

The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.



Memorandum

Date: June 5, 2017

To: Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) Members, Consultants, and Guests

From: Gregory Reaman, MD
Associate Director, Office of Hematology and Oncology Products, CDER, and
Associate Director for Pediatric Oncology, Acting, Oncology Center of Excellence,
FDA

Subject: FDA Background Package for June 22, 2017 Meeting

Thank you for agreeing to participate in the upcoming Pediatric Oncology Subcommittee of the ODAC. The Subcommittee will hear about pediatric development plans for three products that are under development for one or more oncology indications. We believe that this focused discussion will utilize the expertise of the Pediatric Oncology Subcommittee in guiding the Agency's decisions related to the issuance of Written Requests in accordance with current legislative initiatives enacted to accelerate drug development in the pediatric population. The Subcommittee will consider and discuss issues relating to the development of each product for potential pediatric use and provide guidance to facilitate the formulation of Written Requests for pediatric studies, if appropriate. The products under consideration are: (1) Olaratumab, application sponsored by Eli Lilly and Company and (2) Prexasertib, application sponsored by Eli Lilly and Company.

As always, we appreciate your time and commitment and look forward to an informative meeting on June 22, 2017.

REFERENCE:

1. **Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA):**
Title V – Pediatric Drugs and Devices (pages 47-58).

FDASIA legislation is available at: <http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf>

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Pediatric Legislative Initiatives

Pediatric legislation, including a combination of incentives and requirements, has significantly increased pediatric drug research and development and led to a substantial increase in products with new pediatric information in labeling.

Relevant pediatric legislative initiatives are listed below:

- 1997 The Pediatric Exclusivity provision - created in the Food and Drug Administration Modernization Act (FDAMA)
- 2002 Best Pharmaceuticals for Children Act (BPCA) – reauthorization of the Pediatric Exclusivity provision
- 2003 The Pediatric Research Equity Act (PREA - a requirement which allows the FDA to require pediatric studies in drugs and biologics for certain applications
- 2007 Re-authorization of BPCA and PREA in the Food and Drug Administration Amendments Act (FDAAA)
- 2010 The Biologics Price Competition and Innovation Act of 2009 (BPCI) was included in the Patient Protection and Affordable Care Act – created a framework for the approval of follow-on biologics and made biologics, including follow-on biologics, eligible for Pediatric Exclusivity through amendment of section 351 of the Public Health Services Act. BPCI sunsets in March 2015
- 2012 BPCA and PREA made permanent in the Food and Drug Administration Safety and Innovation Act (FDASIA)

Each one of these pediatric milestones has expanded and improved consistency and transparency of the pediatric information available for product use. For example, FDAAA requires that study data, both positive and negative, conducted under BPCA and PREA be described in product labeling. Also, a labeling statement of the FDA's determination whether or not the studies demonstrate safety or efficacy or if the studies were inconclusive in pediatric populations must also be included. Another important milestone with the recent passage of FDASIA was the permanent reauthorization of BPCA and PREA. Other important changes to pediatric drug development were included in this legislation. One such change was the new requirement for drug developers to submit more detailed plans to perform pediatric studies earlier during drug development. Traditionally, drug developers were not required to provide plans for pediatric studies until relatively late the development of a product. New legislation under PREA requires that drug developers submit plans for pediatric drug development earlier during the development of the product (i.e., at the end of phase 2). The intent of this legislation is to promote earlier development of products for pediatric use.

The following is a brief review of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, two laws that support pediatric drug development, and recent changes to these laws under the Food and Drug Administration Safety and Innovation Act.

Best Pharmaceuticals for Children Act

The intent of BPCA is to provide an incentive to drug developers to perform pediatric studies in order to improve the efficacy and safety data available for products used in children and infants. This incentive allows sponsors to qualify for an additional six months of marketing exclusivity for the entire moiety (molecule responsible for the pharmacological action of the drug), if specific studies addressing relevant pediatric indications are completed and submitted to FDA. A Written Request is a document issued by the FDA which outlines the type of studies to be conducted, study design and objectives, and the age groups to be studied. Because the pediatric exclusivity provision is voluntary, the sponsor may decline a Written Request. Thus, FDA has the ability to request that the sponsor perform pediatric studies under a Written Request that can lead to additional marketing exclusivity for the product.

This process can be initiated by either the sponsor or the FDA. A sponsor may submit a Proposed Pediatric Study Request to the FDA to conduct pediatric studies. If the FDA determines there is a public health need, the Agency will issue a Written Request for pediatric studies. These studies may or may not include the studies proposed by the sponsor. FDA may issue a Written Request on its own initiative when it identifies a need for pediatric data.

Of note, prior to 2010, the Written Request process only applied to drugs, and not to biological products. However, under BPCI, biological products became eligible for additional marketing exclusivity through the Written Request process. Since 2012 Written Requests have also been issued for anti-cancer biologic products.

Pediatric Research Equity Act

PREA works in concert with BPCA. In contrast to BPCA, which is based on incentives for drug developers to voluntarily perform needed pediatric studies, PREA requires that pediatric studies must be performed. However, this requirement only applies to the specific indications for which the sponsor is seeking approval for their product. PREA is triggered when an application or supplement is submitted for a new indication, new dosing regimen, new active ingredient, new dosage form, and/or a new route of administration. Under PREA, the FDA may require that the sponsor develop age appropriate formulations for use in required pediatric studies and that the required pediatric studies must include data to support pediatric dosing and administration. Additionally under PREA, pediatric studies of currently marketed drugs and biologics may be required if the product is used by a “substantial” number of children, if adequate pediatric labeling would provide “meaningful” therapeutic benefit compared with existing treatments for children for the claimed indication, or if the lack of “adequate” labeling poses a risk for the pediatric population.

Pediatric studies may be deferred (postponed until a later date) by the FDA in certain situations including if the application is ready for approval for use in adults before pediatric studies are complete, or when additional safety or effectiveness data needs to be collected before studying in the pediatric population. Studies may be waived in full or in part in

certain situations, including when a clinical condition or disease entity does not occur in the pediatric population, when necessary studies are impossible or highly impracticable, when there is evidence strongly suggesting that the product would be ineffective or unsafe in all or some pediatric age groups or when the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and is not likely to be used in a substantial number of pediatric patients.

It should be noted that PREA does not apply to products for indications which have been granted orphan designation. PREA has essentially no applicability for drugs and biologics being developed for oncology as the cancers for which these drugs and biologic products are being developed rarely if ever occur in children. Therefore, pediatric cancers are considered as distinct indications and are subject to study under BPCA through the Written Request mechanism.

Pediatric Study Plan (PSP)

With passage of FDASIA in July 2012, both BPCA and PREA have been permanently reauthorized precluding the necessity of periodic (every 5 years) justification for reauthorization. Among the changes brought by this legislation is the requirement under PREA for earlier initiation of discussion of the proposed studies to be conducted in the appropriate pediatric populations. Sponsors are now required to submit an initial PSP (iPSP) within 60 days of the End of Phase 2 (EOP2) meeting with the FDA. The content of the iPSP includes an outline of the sponsor's proposed study(ies): objectives, design, age groups evaluated, relevant endpoints, and statistical approach. Requests for deferral or waiver may be made with supporting data to justify such request. Relevant information to understand the rationale for the iPSP should be included to describe, as appropriate, a disease overview in the pediatric population and the product under development, potential plans and justification for the use of extrapolation of data generated in other patient populations, nonclinical data both existing and planned to support pediatric studies, plans for pediatric specific formulation when appropriate, synopsis/summary of proposed study(ies) and timelines for completion, information with respect to agreements with other Health Authorities, e.g. Pediatric Investigation Plan(PIP) for EMA. PSPs will be required for all products (drugs and biologics) that trigger PREA if an EOP2 meeting is held as of January 5, 2013.

Additional Provisions of Food and Drug Administration Safety and Innovation Act (FDASIA)

In recognition of the particular need for clinically evaluated drugs in neonates, specific justification for the inclusion or exclusion of neonatal patients in the proposed studies must be provided in the PSP. This information is to be explicitly stated in any Written Request.

Studies that are required under PREA include specific deadlines for completion. Under FDASIA, a new provision allows for an extension of the deadline for submission of these deferred studies. However, the requests for deferral must be reviewed by the Pediatric Review Committee within FDA for recommendations regarding whether the deferral extension should be granted. For studies that have not been submitted prior to the established

deadline, FDASIA has provided increased enforcement mechanisms including the public posting of non-compliance letters for overdue PREA post-marketing requirements and a process for misbranding products, if applicable.

Difficulties in development of drugs for pediatric use in rare diseases have long been an important issue. FDASIA includes a new provision known as the Pediatric Priority Review Voucher. This program awards developers of products for a rare pediatric disease a voucher for 'priority review' of a subsequent human drug application. To qualify for this voucher program, the product and its development program must meet three requirements:

- Definition of a pediatric rare disease; a “disease that primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children and adolescents” and that meets the definition of a “rare disease or condition” set forth under the Orphan Drug Act.
- The application for the voucher “relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population” and
- The applicant “does not seek approval for an adult indication in the original rare disease product application”.

Additionally, within 18 months of the passing of FDASIA, FDA held an open public meeting on the development of new therapies for pediatric rare diseases, including cancer and subsequently sent a Report to Congress on the status of pediatric drug development.

The various pediatric initiatives have led to a dramatic increase in pediatric studies submitted to the FDA and resulted in new pediatric information in labeling. There have been 466 pediatric labeling changes for drugs and biologics between 1998 and October 2012. Of these, 18 labeling changes, including 6 approvals for pediatric use, were for drugs used in oncology.

First Session

PRODUCT: Olaratumab

COMPANY: Eli Lilly and Company

I. Regulatory history

Olaratumab is a recombinant human immunoglobulin G subclass 1 (IgG1)-type monoclonal antibody that binds to platelet-derived growth factor receptor alpha (PDGFR α) and blocks PDGFR α -dependent signaling. Platelet-derived growth factor (PDGF) and PDGFR signaling plays a significant part in mesenchymal biology, including mesenchymal stem cell differentiation, growth, and angiogenesis. The PDGF and PDGFR signaling pathway is also involved in cancer through aberrant cellular signaling and has been implicated in modulating the tumor or stromal microenvironment and facilitating metastases in several malignancies.

In October 2016, Olaratumab given with doxorubicin received accelerated approval for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery. Olaratumab is exempt from all pediatric obligations under the Pediatric Research Equity Act (PREA) in the U.S. as it received an orphan drug designation in October 2014.

During the course of clinical development of olaratumab, 14 Phase 1 or 2 trials have been conducted or are underway, and there is one ongoing Phase 3 trial. This includes eight Phase 1 or Phase 2 trials of olaratumab alone or in combination with chemotherapy in various advanced tumor types. The randomized, open-label, multicenter Phase 2 portion of trial JGDG evaluated the efficacy and safety of olaratumab plus doxorubicin compared to doxorubicin alone in the treatment of adult patients with advanced STS and was the basis for accelerated approval. Olaratumab demonstrated an approximately 12 month improvement in overall survival (HR=0.46, [0.3, 0.71], p=0.0003) as compared to doxorubicin alone when administered at a dose of 15 mg/kg administered intravenously (IV) on Day 1 and 8 of every 21-day cycle. Trial JGDG met the protocol-defined significance level for progression-free survival (PFS) (HR=0.67 [0.44, 1.02], p=0.0615). The most common treatment-emergent adverse events included nausea, fatigue, musculoskeletal pain, neutropenia, mucositis, alopecia, and vomiting. Infusion-related reactions (IRRs) occurred and included one fatal event. Most events occurred in Cycles 1 or 2 and all Grade ≥ 3 IRRs occurred during the first olaratumab dose.

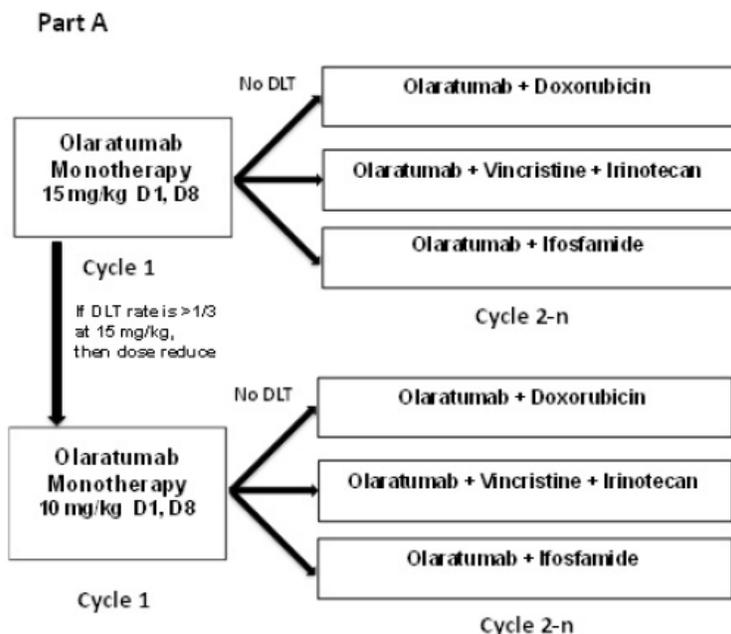
Lilly states that the rationale for the selection of pediatric tumors for evaluation was based on the hypothesis that pediatric sarcomas in which the PDGFR α pathway has been implicated may respond to olaratumab treatment. Data in pediatric patients, suggests that the PDGFR α pathway is overexpressed relative to normal skeletal muscle in both embryonal and alveolar rhabdomyosarcoma (RMS). As per the sponsor, similar PDGFR α pathway activation has also been observed across a series of genetically engineered mouse models of alveolar RMS, which suggests a common requirement of the pathway in RMS pathogenesis. A similar PDGFR α pathway overexpression in both humans and canines has been observed for osteosarcoma, suggesting a biologically important role for the PDGFR α pathway in this disease. Data in

nonclinical studies, suggests olaratumab was active both in vitro and in vivo in pediatric osteosarcoma and rhabdoid tumor. Olaratumab was further evaluated by Lilly in multiple patient-derived xenograft mouse models of pediatric cancer including rhabdomyosarcoma, osteosarcoma, and synovial sarcoma with efficacy observed in osteosarcoma.

The first pediatric clinic trial, I5B-MC-JGDN, is an ongoing, multi-center, open-label, dose-escalation trial of olaratumab as a single-agent and in combination with doxorubicin, vincristine/irinotecan, or high-dose ifosfamide in up to 70 pediatric patients <18 years of age with relapsed or refractory solid tumors that are not amenable to curative treatment. The primary objective is to determine a recommended dose of olaratumab in combination with at least one of the studied chemotherapy regimens in pediatric patients based on any dose-limiting toxicities (DLT), and olaratumab serum exposure-matching between the adult and pediatric populations. Secondary objectives are to investigate the pharmacokinetics of olaratumab as monotherapy and in combination with chemotherapy, and antitumor activity (including objective response rate and PFS) observed with olaratumab in combination with chemotherapy.

The trial will be conducted in two parts. Part A will consist of at least 12 patients. In cycle 1, all patients will receive single-agent olaratumab 15 mg/kg administered IV on Day 1 and Day 8 of the 21-day cycle. Based on the DLT rate, patients will either receive 15 mg/kg of olaratumab in combination with one of three chemotherapy regimens in cycles 2 and beyond, or de-escalate to 10 mg/kg of olaratumab and then receive combination therapy if this dose is tolerated.

Figure 1. Schema of Part A of Study JGDN

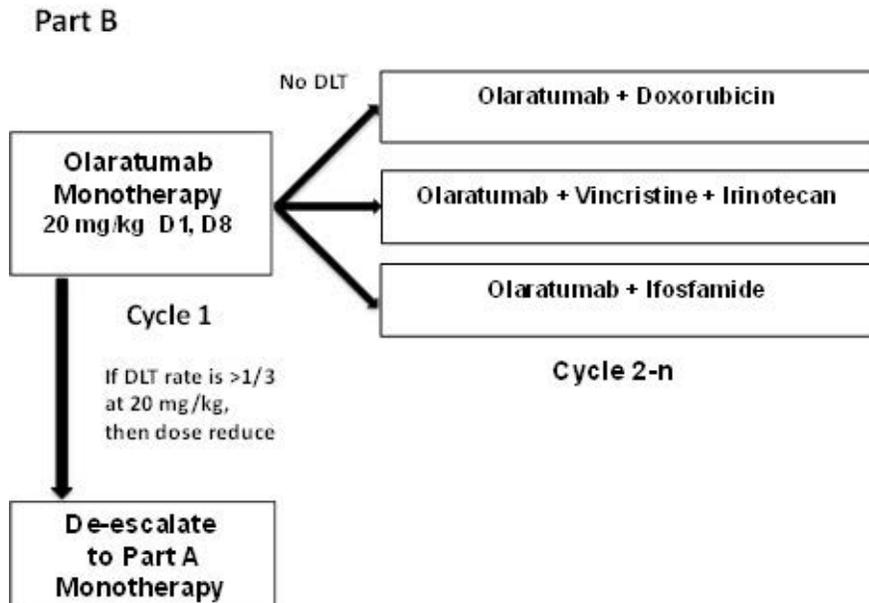


Source: Lilly pediatric ODAC briefing document

Part B will be initiated once safety is established at the first dose level for a given chemotherapy combination arm in Part A. Dose escalation to 20 mg/kg will be evaluated in

Part B. The decision to dose-escalate from 15 mg/kg to 20 mg/kg will be based on safety data collected during the first 2 cycles of treatment of Part A.

Figure 2. Schema of Part B of Study JGDN



Source: Lilly pediatric ODAC briefing document

Radiographic assessments will be performed at baseline and then every 2 cycles until radiographic documentation of progressive disease using REC IST v1.1.

Once pediatric dose and safety are established in Trial JGDN, along with completion of additional nonclinical studies, a future efficacy study is planned, most likely in combination with standard-of-care agents in children with either metastatic osteosarcoma or rhabdomyosarcoma. This efficacy pediatric study would be a multi-center, randomized, placebo-controlled, double-blind study to evaluate safety and efficacy of olaratumab in combination with a standard-of-care chemotherapy regimen. Based on the agreed Pediatric Investigational Plan (PIP), the following tumor types were proposed for possible future efficacy evaluation: advanced or metastatic newly diagnosed osteosarcoma and advanced or metastatic recurrent rhabdomyosarcoma.

II. Issues Relating to the Development of Olaratumab in Pediatrics

1. Based on the non-clinical and clinical data presented, please comment on the relevant cancers that should be included and potential endpoints that should be used in future clinical trials designed to evaluate the efficacy of olaratumab in pediatric patients.
2. Please comment on the safety profile of single-agent olaratumab and possible toxicities that may be seen when olaratumab is added to multi-agent combination therapy in pediatric patients.

3. Please comment on the feasibility of international cooperative group collaboration in the future efficacy study.
4. Please comment on the sponsor's plan to evaluate PDGFR expression in pediatric cancers during their proposed development program.
5. Given the recent approval of this product in adults with STS, please discuss whether evaluation of Olaratumab in pediatric NRSTS should be considered.

Second Session

PRODUCT: Prexasertib
COMPANY: Eli Lilly and Company

I. Regulatory History

Prexasertib is an intravenous small molecule inhibitor of checkpoint kinase 1 (CHK1), a multifunctional protein kinase that regulates DNA replication and the DNA damage response. Chk1 is a multi-functional protein kinase and regulator of cell cycle progression. Inhibition of Chk1 leads to abrogation of DNA repair mechanisms in DNA-damaged tumor cells and results in premature entry into mitosis.

Prexasertib is currently being assessed in seven ongoing clinical trials being conducted by Lilly and five investigator initiated clinical trials (Table 1). Results are available from Trial JTJA and from patients with ovarian cancer in Trial NCT02203513.

Table 1: Ongoing Clinical Trial with Prexasertib

| Protocol Number | Study Sponsor | Study Status | Study Description |
|--------------------|-------------------------------|--------------|---|
| 14D-MC-JTJA (JTJA) | Eli Lilly and Company (Lilly) | Completed | A Dose-escalation study of prexasertib in patients with advanced cancer followed by cohort expansions in patient with squamous cell carcinoma |
| 14D-JE-JTJK (JTJK) | Lilly | Ongoing | A dose-escalation study of prexasertib in Japanese patients |
| 14D-MC-JTJF (JTJF) | Lilly | Ongoing | Dose-escalation followed by cohort expansion of prexasertib in combination with chemotherapy or targeted agents in patients with advanced cancers |
| 14D-MC-JTJI (JTJI) | Lilly | Ongoing | Dose-escalation followed by cohort expansion of prexasertib in combination with chemotherapy and radiation in patients with locally advanced head and neck cancer |
| 14D-EW-JTJG (JTJG) | Lilly | Ongoing | A [¹⁴ C] radiotracer study with prexasertib in patients with advanced cancer |
| 14D-MC-JTJL (JTJL) | Lilly | Ongoing | A dose-escalation study of prexasertib and ralimetinib in patients with advanced cancer followed by cohort expansions of the combination in patients with KRAS or BRAF –mutated colorectal cancer or non-small cell lung cancer |
| 14D-MC-JTJH (JTJH) | Lilly | Ongoing | A Phase 2 study of prexasertib in patients with extensive stage small cell lung cancer who have either platinum-sensitive or platinum resistant/refractory disease |
| NCT02649764 | Investigator | Ongoing | A dose-escalation study of prexasertib in combination with cytarabine and fludarabine in patients with relapsed/refractory acute myelogenous leukemia or high-risk myelodysplastic syndrome |
| NCT03057145 | Investigator | Ongoing | A dose-escalation study of the combination of prexasertib and olaparib in patients with advanced solid tumors |
| NCT02808650 | Investigator | Ongoing | A dose-escalation study of prexasertib in pediatric |

| Protocol Number | Study Sponsor | Study Status | Study Description |
|-----------------|---------------|--------------|---|
| | | | patients with recurrent or refractory solid tumors |
| NCT02203513 | Investigator | Ongoing | A single-arm pilot study of prexasertib in patient with BRAC1-/BRAC2-mutation associated breast or ovarian cancer, non-high-risk triple-negative breast cancer, high-grade serous ovarian cancer at low genetic risk, and metastatic castrate-resistant prostate cancer |
| NCT02873975 | Investigator | Ongoing | A study of prexasertib in patients with solid tumor with replicative stress or homologous repair deficiency |

A total of 146 patients were enrolled in Trial JTJA, the first-in-human, single-agent, dose-escalation trial of prexasertib. Sixty-three patients were enrolled in the dose escalation portion of the trial starting at a dose of 10 mg/m² on days 1 and 3 of a 14-day cycle or 40 mg/m² on day 1 of a 14 day cycle and established the maximum tolerated doses (MTDs) of 40 mg/m² on days 1 and 3 of a 14 day cycle and 105 mg/m² on day 1 of a 14 day cycle. All of the dose-limiting toxicities (DLTs) observed in this clinical trial were hematologic including Grade 4 neutropenia, thrombocytopenia, and/or leukopenia lasting >5 days, Grade 3 thrombocytopenia with bleeding or febrile neutropenia. In the dose expansion, cohort 43 patients were evaluable for response and two patients (4.6%) had a partial response (PR) (both patients with a PR had squamous cell carcinoma one of the head and neck and one of the anus). Given the safety, efficacy, predict target inhibition and PK/PD data obtained during the dose-escalation portion of the study the recommended phase 2 dose (RP2D) was determined to be 105 mg/m² on day 1 of a 14-day cycle.

In the expansion cohorts of Trial JTJA, 83 patients were treated, 57 patients with recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) and 26 with metastatic or recurrent squamous cell carcinoma (SCC) of the anus. Seventy-six of the 83 (92%) patients experienced at least one adverse event and 56 (67%) experienced Grade 4 adverse events. The most common drug-related AEs occurring in >10% of patients included thrombocytopenia (48%), anemia (29%), fatigue (25%), headache (14%). Additional safety data is available from the NCI sponsored trial NCT02203513. This is a pilot study of prexasertib monotherapy in patients with breast cancer, ovarian cancer, and prostate cancer. Results from 32 patients with high-grade serous ovarian cancer have been presented. The most common adverse event observed in these patients was decreased white blood cell count (78%), anemia (66%), and decreased platelet count (34%). Sixty-nine percent of patient experienced transient Grade 4 neutropenia, which resolved to ≤ Grade 2 within 8 days of onset. Two patients (6%) had febrile neutropenia and 56% of patients received G-CSF.

The rationale for the pediatric tumor types in which Lilly plans to develop prexasertib comes from preclinical investigation. Prexasertib has been evaluated in a panel of pediatric tumor cell lines, in more than 25 mouse xenograph models of pediatric or adolescent/young adult tumors, and in the National Cancer Institute's (NCI) pediatric preclinical testing program (PPTP) and pediatric preclinical testing consortium (PPTC). The in vitro screen of prexasertib across a series of pediatric cancer cell lines demonstrated nanomolar sensitivity to prexasertib in cell lines for Ewing sarcoma, neuroblastoma, osteosarcoma, and rhabdomyosarcoma. This sensitivity correlated with increased DNA damage, CHK1 phosphorylation, and MAPK pathway activation. This in vitro screening was confirmed by in vivo testing in mice bearing cell derived xenografts or patient derived xenografts of neuroblastoma, rhabdomyosarcoma, desmoplastic small round cell tumor, Ewing sarcoma, and osteosarcoma (Figure 1). Monotherapy activity was observed in

multiple models of neuroblastoma and the pediatric sarcomas alveolar rhabdomyosarcoma, embryonal rhabdomyosarcoma and desmoplastic small round cell tumor.

Figure 1: Summary of In Vivo Responses to prexasertib Monotherapy in Neuroblastoma and Sarcoma Models

| Tumor Type | Response to Prexasertib |
|-------------------------------------|---------------------------------|
| Neuroblastoma | N=3 CR=2 (67%) PR=1 (33%) |
| Alveolar Rhabdomyosarcoma | N=2 CR=2 *(100%) |
| Embryonal Rhabdomyosarcoma | N=3 CR=1 (33%) PR=1 (33%) |
| Desmoplastic Small Round Cell Tumor | N=1 CR=1 |
| Ewing sarcoma | N=4 SD=1 (25%) |
| Osteosarcoma | N=4 SD=1 (25%) |

Abbreviations: CR, complete response; PR, partial response; SD, stable disease

*Acquired resistance observed

Prexasertib was also evaluated by PPTP and PPTC testing in additional childhood solid tumors and leukemia models. In these evaluation, prexasertib demonstrated in vitro inhibition across multiple cell lines with the most sensitive cell line being MYCN-amplified neuroblastoma.

In addition to the preclinical data showing neuroblastoma's sensitivity to prexasertib, Lilly provides the following biological rationale for neuroblastoma cell lines having sensitivity to prexasertib. The most common genetic alteration in neuroblastoma is amplification of MYCN oncogene, which occurs in 22% of tumors. Overexpression of MYC is associated with elevated replication stress. The ATR-CHK1 pathway is critical for suppression of oncogene-induced replication stress. This association between MYC amplification and the CHK1 pathway is supported by elevated CHK1 expression in MYCN-amplified neuroblastoma tumors. As a result, Lilly hypothesize that tumors with MYCN amplification will have increased sensitivity to a CHK1 inhibitor such as prexasertib.

Similar to neuroblastoma amplification of MYCN has been observed in both alveolar and embryonal rhabdomyosarcoma. Additionally, translocation t(2;13) and t(1;13) resulting in PAX3/FOXO1 and PAX7/FOXO1 fusion genes occur in 80% of alveolar rhabdomyosarcoma and correlate with MYCN amplification or MYCN overexpression in 80% of cases. Lilly reports that the MYCN amplifications and PAX-FOXO1 and PAX7-FOXO1 fusions have the potential to increase replication stress and provide additional rationale for the investigation of prexasertib in rhabdomyosarcoma.

Based on the biologic rationale, the preclinical in vitro and in vivo data as well as the efficacy and safety data for prexasertib in adults, pediatric development has begun with a pediatric dose escalation study sponsored by the Children Oncology Group (COG), entitled A phase 1 study of LY2606368, a CHK 1/2 Inhibitor, in Pediatric Patients with Recurrent or Refractory Solid

tumors including CNS tumors was initiated in March of 2017. The primary objectives of this trial are to estimate the MTD and/or RP2D, define and describe the toxicities of prexasertib, and characterize the PK. Secondary objectives include preliminarily defining the antitumor activity or prexasertib and biomarker assessments. Patients will be enrolled in a rolling six design and treated on days 1 and 15 of a 28-day cycle starting with an initial dose of 80 mg/m². No data from this trial is available to date.

Lilly also plans to conduct a multicenter, nonrandomized, parallel-cohort study of prexasertib in pediatric patients with neuroblastoma or embryonal rhabdomyosarcoma/alveolar rhabdomyosarcoma with relapsed or refractory disease and for whom no standard therapy is available. In this trial, patients will receive prexasertib every 14 days at the RP2D determined in the ongoing phase 1 trial. The primary objective will be to estimate the investigator-assessed objective response rate (ORR). Secondary objectives include assessment of safety, toxicity, PK, biomarker associations, patient-reported outcomes, ORR by independent central assessment, disease control rate, duration of response, event-free survival and overall survival.

Key eligibility criteria include a diagnosis of refractory or relapsed neuroblastoma (Cohort 1) or embryonal or alveolar rhabdomyosarcoma (Cohort 2) who are not appropriate candidates for surgery, radiotherapy or other conventional systemic therapy; age ≥ 12 months and ≤ 21 years of age; measurable disease; adequate performance status as defined by Lansky or Karnofsky; and adequate bone marrow and organ function. The study will enroll approximately 110 patients (55 in each disease cohort, neuroblastoma and rhabdomyosarcoma). For each cohort, if the lower bound of a 95% confidence interval (CI) on the observed objective response rate excludes 15%, the prexasertib will be considered to have superior ORR compared to historical controls. The sample size of 55 patients per cohort will provide at least 80% power to detect an increase in ORR from 15% to 30%.

Additionally, Lilly plans to develop prexasertib in combination with other agents. In nonclinical pediatric models, prexasertib has demonstrated increased efficacy when administered with doxorubicin, cyclophosphamide, or irinotecan. Ongoing trials in adults and data from the safety profile with monotherapy prexasertib will inform the types of cytotoxic chemotherapies agents that can be considered for future pediatric studies. Additionally, Lilly plans to explore combining prexasertib with other targeted agents based on emerging preclinical and adult data.

II. Issues Relating to the Development of Prexasertib in Pediatrics

1. Please consider the preclinical data and rationale for the development of prexasertib in neuroblastoma and rhabdomyosarcoma. Additionally, please discuss other tumor types that may benefit from the development of prexasertib.
2. Please consider the planned pediatric study of prexasertib in neuroblastoma and rhabdomyosarcoma and provide an opinion regarding the overall study design, including the patient population eligible for enrollment and the tumor types that are planned to be evaluated.

3. Please comment on whether rhabdomyosarcoma should be considered one disease or divided into two disease entities for embryonal and alveolar rhabdomyosarcoma given the different pathology and clinical courses of these tumors.
4. Please address any short-term and potential long-term or late toxicities that may be associated with the use of this drug in children.
5. Please address the plans for administering prexasertib in combination with cytotoxic chemotherapy regimens. Please address plans for administering prexasertib in combination with other target therapies.