



FDA Briefing Document

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

June 21, 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 will not include issues relevant to any 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 and sponsor 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 possible 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) APX005M, application sponsored by Apexigen, Inc.; (2) PM01183 (Lurbinectedin), application sponsored by Pharma Mar USA, Inc.; and (3) ASP2215 (Gilteritinib), application sponsored by Astellas Pharma Global Development.

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 21, 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) APX005M, application sponsored by Apexigen, Inc.; (2) PM01183 (Lurbinectedin), application sponsored by Pharma Mar USA Inc.; and (3) ASP2215 (Gilteritinib), application sponsored by Astellas Pharma Global Development.

As always, we appreciate your time and commitment and look forward to an informative meeting on June 21, 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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TABLE OF CONTENTS

1. Pediatric Initiatives.....	4
2. Executive Summaries	
First Session: APX005M	8
Application sponsored by Apexigen, Inc.	
Second Session: PM01183(Lurbinectedin).....	11
Application sponsored by Pharma Mar USA, Inc.	
Third Session: ASP2215 (Gilteritinib),	14
Application sponsored by Astellas Pharma Global Development	

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:

- o 1997 The Pediatric Exclusivity provision - created in the Food and Drug Administration Modernization Act (FDAMA)
- o 2002 Best Pharmaceuticals for Children Act (BPCA) – reauthorization of the Pediatric Exclusivity provision
- o 2003 The Pediatric Research Equity Act (PREA) - a requirement which allows the FDA to require pediatric studies in drugs and biologics for certain applications
- o 2007 Re-authorization of BPCA and PREA in the Food and Drug Administration Amendments Act (FDAAA)
- o 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
- o 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:

- o 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.
- o 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
- o 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: APX005M

COMPANY: Apexigen, Inc.

I. Regulatory history

APX005M is a humanized IgG1κ monoclonal antibody that binds to CD40. *In vitro*, APX005M binds to both human and cynomolgus monkey CD40, triggering activation of B cells, monocytes, and dendritic cells and stimulating cytokine release. APX005M has also demonstrated direct antitumor activity in preclinical models. CD40 is a transmembrane glycoprotein surface receptor member of the tumor necrosis factor receptor (TNFR) superfamily and plays an important role in induction of tumor apoptosis and regulation of immune activation, especially in crosstalk between T cells and antigen-presenting cells (APCs) (Aggarwal, 2003). The CD40 ligand (CD154) is expressed primarily by activated T lymphocytes and platelets, but also dendritic cells, B cells, monocytes, and other non-lymphoid cells (Grewal and Flavell, 1998, Banchereau et al, 1994). Signaling through CD40 on APCs results in antigen processing, presentation, and cytokine release from activated APCs which enhances the T cell response. The Sponsor hypothesizes that a CD40-agonistic antibody can activate and stimulate both innate and adaptive immunity and that these mechanisms do not require CD40 expression on the tumor cells. Furthermore, CD40 is also expressed on multiple different types of tumor cells and can mediate a direct cytotoxic effect; its expression has been reported in 30–70% of primary human solid tumor samples, including melanoma and carcinomas (Eliopoulos and Young, 2004).

The pharmacokinetics (PK), safety, and preliminary assessment of clinical activity of APX005M are being assessed in two ongoing dose escalation/dose expansion studies as monotherapy in adult patients with advanced solid tumors (urothelial carcinoma, melanoma, squamous cell carcinoma of the head and neck, non-small cell lung cancer [NSCLC], or microsatellite instability high (MSIH) tumors) and in combination with nivolumab in adult patients with advanced NSCLC and metastatic melanoma. Apexigen plans to partner with the Pediatric Brain Tumor Consortium (PBTC) for an early phase, multicenter, open-label study designed to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity, and preliminary efficacy of APX005M in children and young adults with malignant brain tumors. The development plan includes the following studies:

- Study PBTC-051 (Proposed Study 1): Two strata (Stratum 1: Histologically confirmed diagnosis of a primary malignant CNS tumor that is recurrent, progressive, or refractory to available treatment; Stratum 2: Newly diagnosed DIPG, 6-14 weeks post-completion of radiation therapy if no evidence of progression). The dose escalation and safety portion

of the study will begin in Stratum 1 in patients aged ≥ 1 and ≤ 21 and will follow a standard 3+3 dose escalation scheme. Once the maximum tolerated dose (MTD)/recommended phase II dose (RP2D) has been established, the total number of patients treated at that dose will be increased to 12. Barring excessive toxicity, approximately 12 DIPG patients will be enrolled in Stratum 2. The first dose level used for the first DIPG cohort will be one dose level below the RP2D determined in non-DIPG patients.

- If preliminary evidence of efficacy is observed in any type of pediatric brain tumor, and if the overall safety profile of APX005M in pediatric patients is acceptable, the results of the study will inform the possible development of APX005M in other pediatric solid tumors and/or in combination with other treatment modalities including immunotherapy.

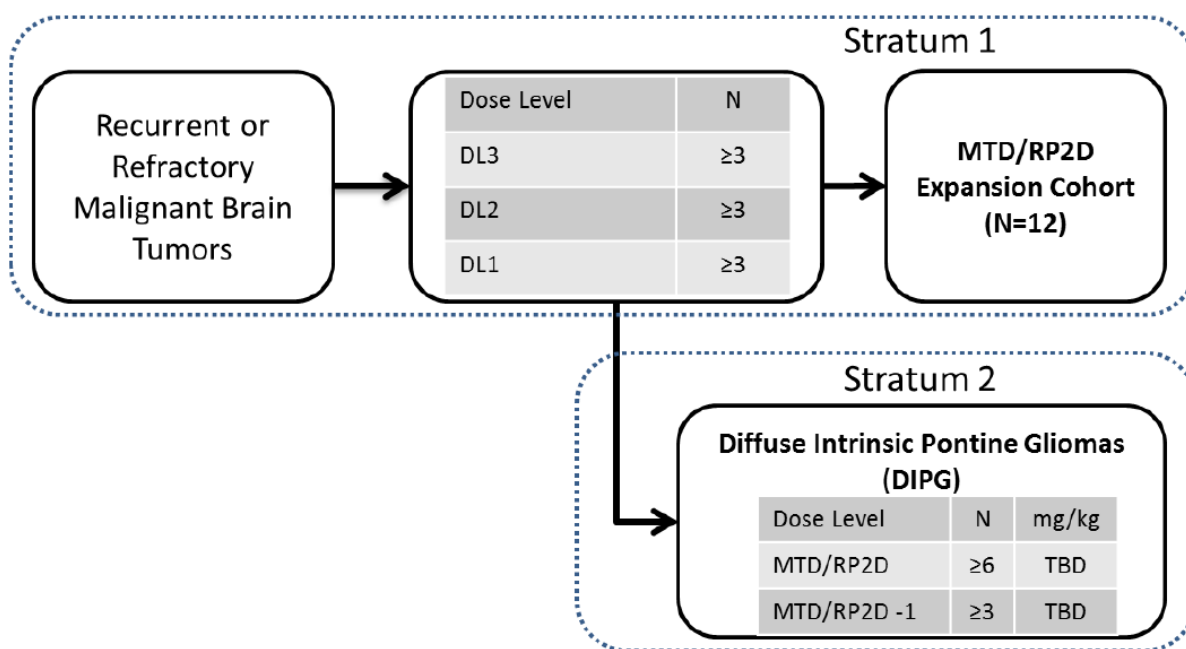


Figure reproduced from Pediatric ODAC Briefing Document

- Proposed Study 2: Randomized, controlled trial to evaluate the safety and efficacy of APX005M in patients from 0 to <18 years of age with a selected malignant solid tumor type determined based on results of Study 1. Elements of study design such as endpoints, choice of comparator, dosage and treatment regimen, sample size and eligibility criteria will depend on the pediatric indication selected. Final protocol and statistical analysis plan for study 2 will be agreed upon with FDA prior to enrollment of the first subject in the study.

II. Issues Relating to the Development of APX005M in Pediatrics

Although several new drugs and biologic agents which target specific key pathways and functions have been developed in pediatrics, in many pediatric cancers the backbone

treatment regimens still consist of cytotoxic agents and compounds which rely on DNA damage for treatment effect. CD40-agonistic antibodies can substitute for CD40L/CD154 on activated T cells to boost immunity and enhance the T cell response through improved antigen processing and presentation. These antibodies can also mediate a direct cytotoxic effect on CD40-expressing tumor cells.

1. Please consider the way in which CD40-agonistic antibodies can be used synergistically with current pediatric cancer treatment modalities, including cancer vaccines, given their immunomodulatory effects.
2. Please comment on the unique safety concerns that arise from the use of immune activator agents, in particular with CD40 agonistic antibodies in pediatric patients, and on methods to mitigate these safety issues in clinical trials.
3. Please consider the importance of evaluating the correlation of tumor cell CD40 expression and antigen burden in various pediatric solid tumors with the activity of CD40-agonistic antibodies, and whether the combined use of CD40-agonistic antibodies with immune checkpoint inhibitors may prove to be useful in tumors with lower CD40 expression and/or antigen burden.

Second Session

PRODUCT: PM01183 (Lurbinectedin)

COMPANY: Pharma Mar USA, Inc.

I. Regulatory History

Lurbinectedin is a synthetic tetrahydroisoquinolone that inhibits DNA transcription. Initiation of the transcription process requires the association of transcription factors to RNA polymerase II; these transcription factors recognize gene promoters and enhancers and thus regulate gene expression. Many cancers are associated with transcriptional dysregulation whereby genetic alterations lead to aberrant expression of genes associated with differentiation, proliferation and survival. Lurbinectedin inhibits transcription by binding to CG-rich sequences, which are mainly located around promoters of protein-coding genes, irreversible stalling of elongating RNA polymerase II on the DNA template which ultimately gets degraded via the ubiquitin pathway, and the generation of DNA breaks leading to apoptosis. Since genetic dysregulation in cancer may be associated with “transcription addiction,” whereby the transcription process is constitutive, Pharma Mar hypothesizes that Lurbinectedin may exert its effect by inhibiting this process in these transcription-addicted tumors.

Beginning in 2008, lurbinectedin has been studied in adults with multiple advanced solid tumors and hematologic malignancies, and fifteen trials are currently ongoing using lurbinectedin alone or in combination with other agents. Preliminary clinical activity has been observed in advanced ovarian cancer, small cell lung cancer (SCLC), breast cancer, and endometrial cancer. In a phase 1 study of single agent lurbinectedin in patients with acute leukemia and MDS (PM1183-A-002-10), there were no response in 35 patients, and 3 patients (2 AML, 1 CMLBP) showed short-term decreases in bone marrow blast counts. In a phase 2 trial (PM1183-N-005-14) using single agent lurbinectedin in patients with advanced solid tumors, 20 patients had tumors in the Ewing Family of tumors (EFT); of the 14 evaluable patients, 3 had a PR for an overall response rate of 21%, and 7 patients had disease stabilization. Lurbinectedin is not yet being studied in any trials in pediatric patients.

As of January 2017, 1204 adult patients have been exposed to lurbinectedin alone or in combination. The most common treatment-emergent adverse events (TEAEs) were hematologic toxicities (neutropenia and thrombocytopenia); this was severe in the initial studies using a flat dose, and led to a BSA-based dosing strategy. Pharma Mar states that the phase 2 studies using the 3.2 mg/m² dose given every 3 weeks appears to be associated with less severe myelosuppression than that seen at the 7 mg dose at the same schedule. Other common TEAEs include gastrointestinal disorders such as nausea and vomiting, and fatigue. Less common TEAEs include decreased appetite, diarrhea, constipation and abdominal pain, as well as pyrexia, dyspnea, phlebitis and stomatitis, most of which were grade 1-2 and responsive to dose modification and/or supportive care. Hepatic function abnormalities were also seen.

The rationale for selection of pediatric tumor types for evaluation was based on the mechanism of action as well as pre-clinical activity in mouse xenograft models. Tissue distribution studies show lurbinectedin distribution that is greatest in the spleen, liver, lymph nodes, thyroid glands, lung, kidney and small intestine, and lowest in the CNS and testes. Neuroblastoma and ewing sarcoma (ES) have been identified by Pharma Mar as having potential for lurbinectedin activity based on the fact that both are “transcription-addicted.” They cite in vitro data that suggests it inhibits MYC, and in-vitro and xenograft data that it inactivates the oncoprotein EWS-FLI1, further supporting its study in these disease settings.

Pharma Mar is exempt from the requirement to conduct pediatric studies under the Pediatric Research Equity Act (PREA) for its indications in ovarian cancer and SCLC. They plan to submit a request to the Paediatric Comittee (PDCO) to confirm whether lurbinectedin is similarly covered by class waivers in ovarian cancer and SCLC by the EMA as well.

Pharma Mar’s planned pediatric development program includes a phase 1, open-label trial of lurbinectedin using a 3+3 design and a modified Fibonacci sequence with primary objectives that include safety, tolerability, pharmacokinetics (PK), and determination of dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) to establish a recommended dose for later phase trials. It will include single-agent as well as possible combination cohorts. Patients with solid tumors that are considered potentially susceptible to the mechanism of action and for which no effective therapy is known will be enrolled. The trial population will consist of patients from 23 months of age through the adolescent age range as they posit that the immature newborn liver would not enable the necessary metabolism of lurbinectedin seen in adult patients, presenting a potential safety issue. They raise the additional 100 ml minimum volume requirement for infusion as another potential safety concern. This study will also obtain preliminary efficacy data in the enrolled population on which decisions regarding continued pediatric development will be based.

Based these efficacy data, phase 2 and 3 portions will proceed as outlined in the table below:

Clinical trials	Phase 1	Phase 2	Phase 3
Objective(s)	Single-agent dose-finding (MTD), the RD and tolerability.	Safety and dose-refinement, as single agent or in combination	Activity, efficacy and safety (benefit/risk).
Design	Single-agent dose escalation, successive cohorts, classical 3+3. In combination (i.e., with DOX).	Single-arm or randomized, according to efficacy observed in phase 1 trials	• Randomized add-on to multi-agent chemotherapy, futility interim analysis. • Randomized, in combination with a front-line treatment regimen.
Population	Solid malignant tumors potentially susceptible to mechanism of action and for which no effective therapy is known. Second or subsequent relapse. Possibly after at least two (failed) treatment attempt using active anti-cancer medicines. Children and adolescents.	• Refractory ES/neuroblastoma with no therapy option. • First relapse of localized ES with unfavorable prognostic factors. • Metastatic ES/neuroblastoma. Possibly restricted to presence or function of marker (biomarker, pharmacogenomic marker, EWS/FLI isoforms).	• First, untreated relapse of ES, and refractory ES with no local treatment option. • Newly diagnosed untreated ES. • First, untreated relapse of neuroblastoma, and refractory neuroblastoma with no treatment option. • Newly diagnosed untreated neuroblastoma.
Dose	Dose escalation. Duration as long as clinical benefit.	• Starting from study 1 (RD). • Different administration schedule(s).	Based on preceding study(ies).
Endpoints	• Acute toxicities. • Cumulating toxicity.	• Antitumor activity (RECIST) by ORR.	Time to event (failure-free, progression-free, event-free

Source: Pharma Mar, USA, Inc. Briefing Document

Clinical trials	Phase 1	Phase 2	Phase 3
	• Pharmacokinetics. • Activity (ORR).	• Pharmacodynamic activity on targets and related pathways.	survival) with supportive overall survival.
Analyses	• Pharmacokinetics. • Modelling of dose including adult data.	Pharmacodynamics and any interaction.	Interim analysis (blinded) on response rates (futility).

DOX, doxorubicin; ES, Ewing sarcoma; MTD, maximum tolerated dose; ORR, overall response rate; RD, recommended dose; RECIST, Response Evaluation Criteria In Solid Tumors.

Source: Pharma Mar, USA, Inc. Briefing Document

II. Issues Relating to the Development PM01183 (Lurbinectedin) of in Pediatrics

1. Please discuss the preliminary pediatric development plan, including the tumor types proposed for further study. In addition, please include considerations regarding a targeted approach based on bio- or other markers versus one that is broader in scope.
2. Given the mechanism of action of lurbinectedin, please consider other pediatric tumor types for which there is a biologic rationale for evaluation of its activity. Address any differences in biology between adult and pediatric hematologic malignancies that might support its study in pediatric diseases for which its activity in adults has been limited.
3. Please discuss the impact of low CNS and testicular penetration of lurbinectedin in tissue distribution studies on potential areas of study in the pediatric population.
4. Please address any potential safety concerns unique to the pediatric population, including consideration as to whether any pediatric age groups should be excluded from study.

Third Session

PRODUCT: ASP2215 (Gilteritinib)

COMPANY: Astellas Pharma Global Development

I. Regulatory History

Approximately 35% of patients with acute myeloid leukemia (AML) harbor mutations of the FMS-like tyrosine kinase 3 (FLT3) gene on chromosome 13q12. These mutations typically result in either an internal tandem duplication (ITD) of amino acids in the juxtamembrane region of the FLT3 protein or, less frequently, a point mutation in the activation loop of the tyrosine kinase domain (TKD). Both ITD and TKD mutations result in constitutive activation of FLT3 kinase. In adults, FLT3-ITD mutations of any length are associated with an increased likelihood of relapse (Schnittger et al, Blood 2002), and FLT3-ITD mutations with a high mutant/wild type ratio are associated with decreased overall survival (OS) (Thiede et al, Blood 2002). Similarly, children with FLT3-ITD AML are more likely to be refractory to primary induction therapy, demonstrate lower rates of progression free survival (PFS) and OS after complete response (CR), and experience higher rates of relapse and subsequent death even if they achieve remission (Meshinchi et al, 2001). The prognostic effect of FLT3-TKD mutations is still under debate, and may be dependent on additional mutations in individual patients (Bacher et al, Blood 2008).

Gilteritinib is a pyrazinecarboxamide derivative that inhibits wild-type and mutant (ITD and D835 TKD) FLT3 with nanomolar potency (Lee et al, Blood 2017). Gilteritinib also inhibits AXL, leukocyte receptor tyrosine kinase (LTK), and anaplastic lymphoma kinase (ALK) at similar concentrations (Sponsor's briefing package). The Sponsor hypothesizes that gilteritinib will improve outcomes in patients with FLT3-mutated AML. This hypothesis may be supported by the recent FDA approval of midostaurin (a multi-kinase inhibitor with activity against WT and mutant FLT3) in combination with intensive chemotherapy in adults with newly diagnosed, FLT3-mutated AML based on improved overall survival compared to chemotherapy alone.

The pharmacokinetics, safety and preliminary efficacy of gilteritinib was tested in 252 adults with relapsed or refractory AML who enrolled in the first-in-human trial. FLT3 mutation was not an eligibility requirement. The maximum tolerated dose was determined to be 300 mg PO once daily due to diarrhea and hepatic toxicity at higher dose levels. Diarrhea (16%) and fatigue (15%) were the most commonly reported treatment-related adverse events of any grade (Perl et al, ASH 2016). The most common grade ≥ 3 adverse events were febrile neutropenia (40%), anemia (25%), platelet count decreased (15%), sepsis (14%) thrombocytopenia (13%) and pneumonia (12%). The most common serious adverse events were acute renal failure (2%), blood creatine phosphokinase increased (2%), febrile neutropenia (2%), and AST increased (2%). The most common events leading to treatment discontinuation were sepsis (3%) and respiratory failure (2%). There were 7 fatal adverse events with possible or probable attribution to gilteritinib: intracranial hemorrhage, pulmonary embolism, hemoptysis, septic shock, neutropenia, ventricular fibrillation and respiratory failure. Identified risks of gilteritinib are posterior reversible encephalopathy syndrome, which occurred in two patients, QT prolongation,

elevated creatine kinase and muscle-related adverse events, and elevated liver transaminases (Sponsor's briefing package).

A total of 191 adults with FLT3-mutated relapsed or refractory AML, the majority with FLT3-ITD mutations, were treated on the study. Most received doses of either 120 mg or 200 mg daily as part of two dose-ranging expansion cohorts. The overall response rate (ORR) was 49% (93/191) and the complete response (CR) rate was 9.4% (18/191), with responses occurring at similar frequencies across dose levels ranging from 80 mg to 300 mg daily. The median duration of response was 112 days. The recommended dose for further testing in adults is 120 mg PO once daily (Sponsor's briefing package).

The Sponsor's planned pediatric development program includes two clinical trials, one in children age ≥ 2 with relapsed or refractory FLT3/ITD positive AML (Study 0603) and the other in children age ≥ 2 years with newly diagnosed FLT3/ITD positive AML (Study 0604). In both studies, gilteritinib will be administered in combination with chemotherapy. Due to nonclinical data suggesting that gilteritinib could affect the development of the heart in newborns and infants via inhibitory effects on the serotonin 5HT2B receptor, the Sponsor proposes that gilteritinib not be used in children < 6 months of age. If the results of a planned juvenile toxicology study are supportive, the Sponsor plans to add children between the ages of 6 months and 2 years to the planned pediatric trials. Two pediatric formulations are planned: 10mg mini-tablets (1/4 the size of the adult tablets) and an oral suspension created from the mini-tablets.

Study 0603 is designed to assess the safety and efficacy of gilteritinib in combination with fludarabine, cytarabine, GCSF and liposomal Daunorubicin (FLAG-DNX) in children with relapsed or refractory AML (Figure 1). It will enroll approximately 9 patients in the dose-finding phase 1 and up to another 40 patients in a two-stage phase 2. The primary endpoint is the CRc rate after 2 cycles of gilteritinib + induction chemotherapy; it will be evaluated based on a null hypothesis CRc rate of 35%. The Sponsor is in discussions to conduct this trial in partnership with a pediatric oncology cooperative group.

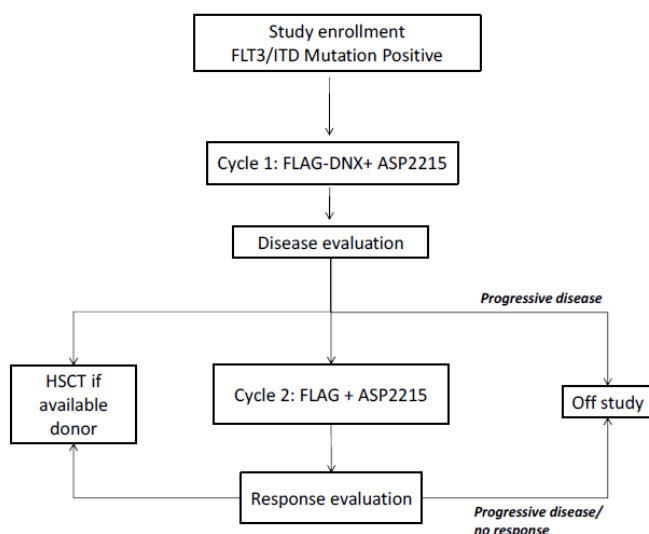


Figure 1

Study 0604 is designed to assess the safety and efficacy of gilteritinib in combination with standard chemotherapy and/or standard chemotherapy plus a non-specified experimental chemotherapy in children with previously untreated AML. Approximately 56 pediatric patients will enroll on Arm C. The primary endpoint is event-free survival (EFS) at 2 years after initiation of treatment (Figure 2), which will be compared to a null hypothesis EFS of 41% (the observed 2-year EFS for trial AAML0531 Arm A patients with FLT3/ITD positive AML). The study is planned as a piggyback onto a larger phase 3 study being conducted by a cooperative group that compares a standard chemotherapy arm to an experimental arm. Children who test positive for FLT3-ITD on that study will be offered participation on Study 0604, in which gilteritinib would be added to existing protocol-defined therapy.

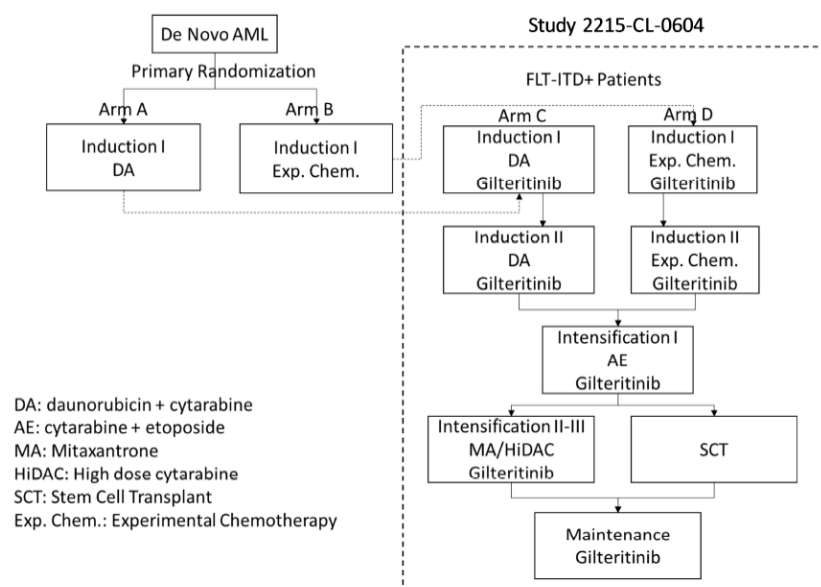


Figure 2

II. Issues Relating to the Development of Gilteritinib in Pediatrics

1. Please discuss the preliminary pediatric development plan, including the indications proposed for further study and, in particular, the proposal to study gilteritinib only in children with AML and FLT3-ITD.
2. Please discuss any potential safety concerns unique to the pediatric population, including toxicities that may be seen when gilteritinib is added to multi-agent chemotherapy. Consider whether any pediatric age groups should be excluded from study and mechanisms to minimize risk on the proposed clinical trials.
3. Please comment on the sponsor's proposal to include one year of maintenance therapy with gilteritinib monotherapy after Intensification II or HSCT in Study 0604.

References:

Backer U, Haferlach C, et al. Prognostic relevance of FLT3-TKD mutations in AML: the combination matters – an analysis of 3082 patients. *Blood* (2008) 111:2527-2537.

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