



FDA Briefing Document

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

November 1, 2011

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 topic, “Pediatric Development Plans of Four Oncology Products”, 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. 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: October 5, 2011

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

From: Richard Pazdur, MD
Director, Office of Hematology and Oncology Products, CDER, FDA

Subject: FDA Background Package for November 1, 2011 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 four products that were either recently approved by FDA, are in late stage development for an adult oncology indication, or in late stage development in pediatric patients with cancer. 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 pediatric use and provide guidance to facilitate the formulation of Written Requests for pediatric studies, if appropriate. The four products under consideration are: (1) sodium thiosulfate injection, application submitted by Adherex Technologies, Inc.; (2) vismodegib (GDC-0449), application submitted by Genentech, Inc.; (3) pazopanib, application submitted by Glaxo Wellcome Manufacturing Pte Ltd, Singapore doing business as GlaxoSmithKline; and (4) Medi-573 (fully human antibody to IGF-I and IGF-II), application submitted by MedImmune, LLC.

As always, we appreciate your time and commitment and look forward to an informative meeting on November 1, 2011.

REFERENCE:

1. **Food and Drug Administration Amendments Act of 2007 (FDAAA):** Title IV – Pediatric Research Equity Act Of 2007 (pages 44-54) & Title V – Best Pharmaceuticals For Children Act Of 2007 (pages 54-68).

FDAAA legislation is available at:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049870.pdf>

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Pediatric Initiatives

Pediatric Initiatives Including the Best Pharmaceuticals for Children Act, the Pediatric Research Equity Act and the Pediatric Rule

Historically, children were excluded from clinical trials for numerous reasons and therefore most drug and biological products lacked adequate pediatric information in labeling. Recent 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.

The Pediatric Exclusivity provision is an incentive program originally created in the Food and Drug Administration Modernization Act of 1997 (FDAMA), and reauthorized in January 2002, as the Best Pharmaceuticals for Children Act (BPCA). The Pediatric Research Equity Act (PREA), signed into law in December 2003, is a requirement which allows the FDA to require pediatric studies for certain applications. BPCA and PREA were reauthorized in September 2007, in the Food and Drug Administration Amendments Act (FDAAA), which sunsets on October 1, 2012.

FDAAA requires that the labeling resulting from studies conducted under BPCA and PREA include information on the pediatric studies and a statement of the FDA's determination whether or not the studies demonstrate safety or efficacy or if the studies were inconclusive in pediatric populations.

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 almost 400 pediatric labeling changes for drugs and biologics between 1998 and August 2010.

Best Pharmaceuticals for Children Act (Incentive - Voluntary)

The Pediatric Exclusivity provision allows sponsors to qualify for an additional six months of marketing exclusivity, which attaches to the entire moiety (molecule responsible for the pharmacological action of the drug) not just the drug studied, if the sponsor completes and submits to FDA pediatric studies as outlined in a Written Request. This is a big carrot. The Pediatric Exclusivity would apply to all of the sponsor's formulations, dosage forms and indications for which the moiety is approved.

A Written Request is a specific 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. The Pediatric Exclusivity process can be initiated by either the sponsor or the FDA. A sponsor may submit a proposal 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. More than 170 drugs have been granted exclusivity as of August 2010.

Of note, the Pediatric Exclusivity provision originally only applied to drugs.

On March 23, 2010, the Patient Protection and Affordable Care Act which included the “Biologics Price Competition and Innovation Act of 2009” (“Biologics Act”) was signed into law. The Biologics Act created a framework for FDA approval of follow-on biologics. The Biologics Act amended section 351 of the Public Health Services Act to make biologics, including follow-on biologics, eligible for Pediatric Exclusivity. The Biologics Act sunsets in March 2015.

Pediatric Research Equity Act (Requirement)

In December 2003, PREA was signed into law. PREA codified many of the provisions of the Pediatric Rule, a regulation issued by the FDA in December 1998 that required that any new drug application or supplement contain an assessment of the drug or biological product in the pediatric population at the time of submission, unless a waiver or deferral was granted. The Rule was suspended by court order on October 2002. PREA works in concert with BPCA. In contrast to BPCA, which provides a voluntary mechanism for obtaining needed pediatric studies on either approved or unapproved indications for a given drug, PREA requires pediatric studies but only in the indications for which the sponsor is seeking approval. 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. The sponsor must use age appropriate formulations and the studies must include data to support pediatric dosing and administration. 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. PREA does not apply to products granted orphan designation.

Pediatric studies are often started after adult studies are complete. Therefore, most pediatric studies are not submitted when the product is initially approved in adults. Discussions with FDA on developing pediatric plans and initiating pediatric studies should occur early in the product development process. 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 (requirement released) in full or in part in certain situations, including when necessary studies are impossible or highly impracticable, there is evidence strongly suggesting that the product would be ineffective or unsafe in all or some pediatric age groups or 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.

SESSION 1

PRODUCT: Sodium thiosulfate injection
COMPANY: Adherex Technologies, Inc.

I. Regulatory History

Cisplatin is an important component of the chemotherapeutic backbone for many pediatric solid tumors. Cisplatin induced ototoxicity is a common and serious adverse event associated with treatment. The impact of ototoxicity in the pediatric age group is significant especially when considering its lasting effects on language development.

The Children's Oncology Group (COG) is conducting ACCL0431, a multicenter, phase 3 study of sodium thiosulfate for the prevention of cisplatin-induced ototoxicity in children. Pediatric patients with newly diagnosed cancer requiring intensive cisplatin therapy are eligible. Pediatric patients with hepatoblastoma, germ cell tumor, osteosarcoma, neuroblastoma, medulloblastoma, and other cancers requiring cisplatin therapy are expected to enroll. Primary endpoints include the incidence of hearing loss between the STS and observations arms as defined by American Speech-Language-Hearing Association criteria at 4 weeks post completion of cisplatin therapy. Secondary endpoints include event free survival and overall survival. An additional secondary endpoint includes an optional biology study to evaluate the possibility of differential otoprotection by STS in patients with variations of the thiopurine S-methyltransferase (TPMT) and catechol O-methyltransferase (COMT) enzymes.

The International Childhood Liver Tumour Strategy Group, SIOPEL, is conducting a multi-country, open-label randomized phase 3 trial of the efficacy of sodium thiosulfate in reducing ototoxicity in patients receiving cisplatin chemotherapy for standard risk hepatoblastoma. The rate of Brock grade ≥ 1 hearing loss determined after the end of trial treatment or at an age of at least 3.5 years whichever is later is the trial primary endpoint. Secondary endpoints include event free survival and overall survival.

II. Issues with the development of sodium thiosulfate in pediatrics.

As designed, will these trials provide adequate evidence of efficacy in preventing cisplatin-related hearing loss? In addition, since these studies are not designed to address the issue of possible tumor protection, do you feel that additional studies are required to assure that overall survival and event free survival are not negatively impacted by STS therapy? If so, what trial design would the committee suggest for further study?

SESSION 2

PRODUCT: Vismodegib (GDC-0449)

COMPANY: Genentech, Inc

I. Regulatory History

Vismodegib is an orally administered inhibitor of the hedgehog pathway. Vismodegib is currently under investigation for the treatment of patients with advanced basal cell carcinoma (BCC) for whom surgery is inappropriate. In pediatric oncology, constitutively activated expression of Sonic hedgehog (SHH) in cerebellar granule neural cell progenitors has been implicated in the pathogenesis of medulloblastoma. Furthermore, SHH inhibition with small molecule drugs has blocked medulloblastoma growth both *in vitro* and in mouse models with constitutively activated SHH. SHH signaling also plays an important role in the embryonic neural crest cell development; more recent *in vitro* studies have suggested that SHH expression may contribute to the development of neural crest cell-derived neuroblastoma.

II. Issues Relating to the Development of vismodegib in Pediatrics

1. Based upon review of the briefing documents, are pediatric studies of vismodegib warranted?
2. If pediatric studies of vismodegib are warranted, please identify the pediatric cancers and pediatric subpopulations (e.g., ages, degree of refractoriness to therapy) that should be targeted for drug development.

SESSION 3

PRODUCT: Pazopanib

**COMPANY: Glaxo Wellcome Manufacturing Pte Ltd, Singapore
doing business as GlaxoSmithKline**

I. Regulatory History of the Drug:

VOTRIENT (pazopanib) is a tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor VEGFR-1, VEGFR-2, VEGFR-3, platelet derived growth factor receptor (PDGFR)- α and- β , and c-kit tyrosine kinases. Pazopanib received regular approval for the treatment of patients with advanced renal cell carcinoma on October 19, 2009. More recently data from a randomized, double blind study performed in adults with metastatic soft tissue sarcoma showed an improvement in median PFS for patients treated with pazopanib in comparison to placebo (median: 20 vs. 7 weeks; HR=0.31, 95% CI 0.24-0.40; P<0.0001). Most patients had progressed following previous treatment with anthracycline containing regimens.

II. Issues Relating to the Development of pazopanib in Pediatrics

A. Non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) comprise 4% of pediatric malignancies and affect approximately 500 patients younger than 20 years old in the US each year. Despite advances in other areas of pediatric oncology, the cure rate for this subset of patients has remained unchanged in more than 2 decades with little change in traditional chemotherapy approaches. Studies in these patients are usually complicated by the rarity of individual subtypes of NRSTS and the lack of response to chemotherapy consisting of anthracyclines and alkylators. Development of novel approaches to treatment of NRSTS is critical to improving the outcomes for this patient population.

1. Does the panel consider pazopanib a viable drug candidate for further study in pediatric and young adult patients with non-rhabdomyosarcoma soft tissue sarcomas (NRSTS)?

a. Please comment on potential study designs.

B. Rhabdomyosarcoma is the most common soft tissue sarcoma in children and adolescents affecting nearly 250 patients in the US annually. Although cure rates for most subtypes of rhabdomyosarcoma have drastically improved with multimodal therapy, patients with relapsed and metastatic disease continue to fare poorly despite attempts at treatment intensification with cytotoxic chemotherapy. Up-front window approaches for testing new agents in rhabdomyosarcoma have in the past helped identify active agents and agent combinations. This approach however has not led to any improvements in survival rates of patients with high risk disease. Novel therapeutic approaches with targeted agents may offer an alternative approach worthy of further exploration in this patient population.

2. Does the panel consider pazopanib a viable drug candidate for further study in pediatric and young adult patients with rhabdomyosarcoma?
 - a. Please comment on potential study designs.

SESSION 4

PRODUCT: Medi-573 (fully human antibody to IGF-I and IGF-II)

COMPANY: MedImmune, LLC

I. Regulatory History

Insulin-like Growth Factor 1 Receptor (IGF1R) signaling is believed to play a crucial role in the etiology of soft tissue and bone sarcomas, and in particular, in the development of sarcomas commonly seen in the pediatric age group. Multiple monoclonal antibodies and small molecule inhibitors targeting this pathway are currently in different phases of clinical development. Results from early phase studies in heavily pretreated patients with relapsed/refractory sarcomas (notably Ewing Sarcoma Family of tumors) suggest that these agents may have modest activity. However there are currently no definitive plans for late phase development of many of these agents due to lack of efficacy in more prevalent adult cancers.

MEDI-573 is a human immunoglobulin G2 lambda (IgG2 λ) monoclonal antibody (MAb) that targets the insulin like growth factor (IGF)-I and IGF-II ligands, thus inhibiting the insulin-like growth factor receptor (IGF-1R) as well as insulin receptor A isoform (IR-A) signaling pathways. This mechanism of action differs from most other agents currently under development that directly inhibit IGF-1R. This agent is currently under investigation in adults but has not been tested in pediatric patients.

II. Issues Relating to the Development of MEDI-573 in Pediatrics

1. Do you consider the modest activity of IGF1R inhibitors seen to date sufficiently compelling to warrant more definitive evaluation in children, adolescents, and young adults with specific sarcoma subtypes? Specifically, how do you think the different mechanism of action of MEDI-573 impacts further investigation of this agent in bone and soft tissue sarcomas in children, adolescents, and young adults?
2. What recommendations do you have regarding the most appropriate pediatric patient population(s) in which to study these agents?
3. What recommendations do you have regarding the appropriate study design to efficiently evaluate the safety and activity of this class of agents in this pediatric population?