FDA Briefing Document

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)
June 20, 2019
Afternoon Session

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 one product in early 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 product under consideration is ONC201, presentation by Oncoceutics, Inc.

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Memorandum

Date: May 23, 2019

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 20, 2019 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 one product that is 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 this product for potential pediatric use and provide guidance to facilitate the formulation of Written Requests for pediatric studies, if appropriate. The product under consideration is ONC201, presentation by Oncoceutics Inc.

As always, we appreciate your time and commitment and look forward to an informative meeting on June 20, 2019.

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)
- 2017 Title V of the Food and Drug Administration Reauthorization Act (FDARA) (FD&C Act Sec. 505B (a)(3), 21 USC 355c (a)(3), Public Law 115-52) RACE for Children Act

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.

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.

Currently, BPCA and the Written Request Process is the only legislative initiative relevant to the pediatric oncology population. Therefore, we attempt to maximize regulatory authority through BPCA to accelerate the development of potentially effective new therapies for children with cancer.

ONC201

PRODUCT: ONC201
COMPANY: Oncoceutics Inc.

I. Regulatory history

ONC201 is a small molecule that antagonizes dopamine receptor D2 (DRD2), a G protein-coupled receptor. DRD2 inhibits adenylyl cyclase activity and impacts signaling cascades that promote cancer cell survival, angiogenesis, and migration. DRD2 is overexpressed in several types of cancer including high grade gliomas (HGGs), particularly H3 K27M-mutant gliomas, and is generally associated with worse prognosis. H3 K27M is a histone 3 (H3) gene mutation that identifies midline gliomas including diffuse intrinsic pontine gliomas (DIPG). These HGGs have historically been inoperable due to the critical physiological functions occurring in the midline region of the brain. No therapeutic interventions have been shown to prolong survival in patients with H3 K27-mutant glioma other than radiation therapy.

ONC201 is reported to activate the integrated stress response (ISR) in malignant cells and result in downstream effects including induction of apoptotic genes via downregulation of Akt and ERK signaling. The study drug has induced cell death in a variety of tumors harboring diverse mutations in several genes including *p53, KRAS, Raf* and *EGFR*. Anti-tumor activity has been demonstrated in a range of pre-clinical studies including solid and liquid tumors (e.g., colorectal cancer [CRC], triple negative breast cancer [TNBC], non-small cell lung cancer [NSCLC], intracranial glioblastoma [GBM], lymphoma and multiple myeloma).

The first clinical investigation of ONC201 was a dose-escalation and dose expansion trial designed to assess safety and preliminary efficacy in adult patients with advanced solid tumors (CRC, TNBC, NSCLC, GBM). No dose-limiting toxicities were observed in this study and a biologically optimal dose of 625 mg once every three weeks was established. ONC201 crosses the blood-brain barrier and is being evaluated in multiple dose-finding and activity-estimating trials in adults with select cancers including HGG, relapsed/refractory multiple myeloma, recurrent neuroendocrine tumors, recurrent endometrial cancer, relapsed/refractory non-Hodgkin lymphoma, and hematologic malignancy. Oncoceutics reports that the study drug has exhibited a favorable safety profile at recommended phase 2 dose (RP2D) of 625 mg orally once every week with no drug discontinuation due to drug-related toxicity.

In the study of ONC201 in adult patients with recurrent GBM (Study ONC006; NCT02525692), one patient experiencing an extensively durable response was noted to have a tumor harboring the H3.3 K27M mutation with DRD2 overexpression and suppressed DRD5 expression. Subsequently, Oncoceutics initiated a dedicated clinical trial for adult patients with recurrent HGG with confirmed H3 K27M mutation (Study ONC013; NCT03295396). Of the fifteen patients enrolled in this ongoing study, best response by criteria for HGG or low-grade glioma (LGG) is reported to yield the following results: two patients with complete response (CR), two patients with partial response (PR), and three patients with minor response (MR).

The only current clinical development of ONC201 in pediatrics consists of a single, ongoing dose escalation and expansion study in patients age 2 to less than 19 years old with newly diagnosed DIPG and recurrent/refractory H3 K27M-mutant gliomas (Study ONC014; NCT03416530). The primary endpoint in this open-label, multicenter trial is to determine the RP2D of ONC201 as a single agent and in combination with radiation in pediatric patients. There are five arms (A-E) in this study with an anticipated enrollment of 93 patients. The study population includes patients with glioma who are positive for the H3 K27M mutation and have completed at least one line of prior therapy, patients with newly diagnosed DIPG with or without H3 K27M mutation and patients with midline gliomas. Dosing is based on body weight with scaling of the adult fixed dose. ONC201 is being provided as capsules for four arms and as a liquid formulation for one arm of the trial. Thus far, Arm A (n=21), consisting of patients with H3 K27M-mutant gliomas, has completed accrual and the RP2D has been confirmed as 625 mg once per week. Nausea and headache were the most commonly observed low-grade adverse events possibly attributed to the ONC201. Oncoceutics reports a single grade 3-4 adverse event of aspartate aminotransferase elevation as possibly related to the study drug. There is also a multicenter, expanded access program to provide ONC201 to patients with previously treated H3 K27M-mutant gliomas who are ineligible for or unable to receive ONC201 through clinical trials.

Additional pediatric clinical studies are in development and include trials that will further evaluate efficacy of the investigational agent in the aforementioned brain tumors. One such trial designed in collaboration with a cooperative group will assess ONC201 in combination with radiation in pediatric patients with newly diagnosed DIPG and H3 K27M-mutant glioma based on a primary endpoint of overall survival compared to matched historical controls. Oncoceutics reports that the potential utility of ONC201 in pediatric indications other than HGGs is being evaluated in preclinical studies in collaboration with the NCI Pediatric Preclinical Testing Consortium.

II. Discussion Issues Relating to the Development of ONC201 in Pediatrics

1. Given the mechanism of action of ONC201 and broad antitumor activity observed in a range of preclinical cancer models, please consider possible options for evaluation of ONC201 in pediatric pre-clinical tumor models and possible pediatric development of ONC201 beyond HGGs.
2. Please discuss the CNS penetration properties of ONC201 and any potential role in addressing brain metastases in children.
3. Please consider the plans for administering ONC201 in combination with other treatments such as radiation therapy, targeted therapies or chemotherapy regimens and recommendations for isolating the effect of ONC201.
4. Please address any potential short-term or long-term toxicity unique to the pediatric population that might justify exclusion of any pediatric age groups not planned for study (e.g., patients younger than 2 years of age are ineligible in ongoing Study ONC014).
5. Please comment on the potential endpoints that could be used in future clinical trials designed to evaluate the isolated efficacy of ONC201 in pediatric patients.