FDA Briefing Document

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

June 29, 2016
Morning 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 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.

Issue: Information will be presented to gauge investigator interest in exploring potential pediatric development plans for two 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) LOXO-101, presentation by Loxo Oncology, Inc., and (2) Entrectinib, presentation by Ignyta, 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: June 3, 2016

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

From: Gregory Reaman, MD
Associate Director for Oncology Sciences, Office of Hematology and Oncology Products (OHOP), CDER, FDA

Subject: FDA Background Package for June 29, 2016 Morning Session

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Thank you for agreeing to participate in the upcoming Pediatric Oncology Subcommittee of the ODAC. The Subcommittee will hear about pediatric development plans for two 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 two products under consideration are: (1) LOXO-101, presentation by Loxo Oncology, Inc., and (2) Entrectinib, presentation by Ignyta, Inc.

As always, we appreciate your time and commitment and look forward to an informative meeting on June 29, 2016.

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

Pediatric Oncology Subcommittee of the
Oncologic Drugs Advisory Committee (ODAC)
November 19, 2015
FDA Briefing Document

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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 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.

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. To date, no Written Requests have been issued for 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, 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.

In should be noted that PREA does not apply to products granted orphan designation. PREA has limited applicability for drugs and biologics being developed for oncology as the tumors being treated in adults rarely occur in children. Therefore pediatric tumors are considered as distinct indications and are studied by a Written Request under BPCA.

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 within 60 days of the End of Phase 2 (EOP2) meeting with the FDA. The content of the PSP 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 information. Relevant information to understand the rationale for the PSP 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 subjects 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 and 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 has subsequently prepared 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, 15 labeling changes, including 4 approvals for pediatric use, were for drugs used in oncology.

First Session

PRODUCT: LOXO-101
COMPANY: Loxo Oncology, Inc.

I. Regulatory history

LOXO-101 is a selective adenosine triphosphate (ATP) competitive inhibitor of the tropomyosin-related kinases (TRK), TRKA, TRKB, and TRKC. In cancer, the neurotrophic TRK (NTRK) genes, which encode for the TRK kinases are subject to dominant oncogenic activating rearrangements (fusions) that lead to constitutive activation of downstream signaling pathways. LOXO-101 blocks the ATP binding site of the TRK family of receptors with enzyme affinities in the low nanomolar range and has shown tumor regression in both in vitro and in vivo non-clinical cancer models.

NTRK fusions are rare and occur across a number of tumor histologies. The first report of an NTRK-fusion was described in colorectal cancer and since that time NTRK mutations have been identified in a wide range of commonly occurring tumors such as lung cancer, thyroid cancer, and sarcomas. In pediatric tumors, NTRK gene fusions occur either at a high frequency in rare tumors or at a low frequency in more common tumors. Table 1 summarizes the overall incidence of pediatric tumors with NTRK fusions.

Table 1: Overall Incidence of Tumors with NTRK Fusions

Tumor Type	Estimated 2013 Incidence*	Metastatic/Locally Advanced/Recurrent Potential	Percentage of NTRK fusion
Infantile Fibrosarcoma (IFS)	0.1 per 1 million	Extremely low	> 75%
Cellular Subtype Congenital Mesoblastic Nephroma (CMN)	0.08–0.4 per 1 million	Extremely low	> 90%
Pediatric Papillary Thyroid Carcinoma (PTC)	5.3 per 1 million	Low	~ 25%
Pediatric Spitzoid Tumors	0.005–0.02 per 1 million	Extremely low	~ 25%
Pediatric Primary Central Nervous System (CNS) Disease	30.8 per 1 million	Extremely high	~ 10%
Pediatric Soft Tissue Sarcoma (STS)	9.6 per 1 million	High	< 1%

Sources: (Cotignola, Reva et al. 2007) (Forman, Ferringer et al. 2008) (Wang, Li et al. 2014) (Sebire and Vujanic 2009) (Furtwaengler, Reinhard et al. 2006) (Santos, Carvalho Jde et al. 2011) (Swetter, Boldrick et al. 2005).

*The incidence and prevalence of various tumors were investigated using data from the SEER from the NCI (SEER, released April 2016) and the scientific literature. Appropriate SEER codes were available from the International Classification of Childhood Cancer (ICCC) Recode ICD-O-3/ WHO 2008 classification system (http://seer.cancer.gov/iccc/iccc-who2008.html). Incidence calculations were made using the SEER*STAT program Surveillance Research Program, National Cancer Institute (SEER*Stat software (www.seer.cancer.gov/seerstat; version 8.3.2.). However, not all tumors could be identified in SEER*STAT so literature was used to aid in estimating the incidence and prevalence. Incidence figures were age-adjusted to the 2000 US standard Population (single ages to 84; Census P25-1130) standard.

Source: copied from Loxo Oncology Briefing Package

The diversity and rarity of NTRK gene fusions represents the most difficult challenge in the development of LOXO-101 for pediatric patients. NTRK is not routinely screened for in the pediatric clinical setting. LOXO Oncology reports that in order for the efficient development of LOXO-101 to proceed widespread adoption of comprehensive genomic profiling in pediatrics, with methods sensitive for NTRK gene fusion detection, need to be adopted to identify patients who might benefit from receiving LOXO-101.

LOXO-101 is currently being evaluated in four clinical trials: An Adult Phase 1 dose escalation study in patients with advanced cancers (LOXO-TRK-14001), an adult Phase 2 basket study in NTRK fusion-positive tumors (LOXO-TRK-15002), and a Phase 1 dose escalation study in pediatric advanced cancer patients (LOXO-TRK-15003). LOXO-101 is also included in the NCI-Molecular Analysis for therapy Choice (NCI-MATCH) trial which will begin enrollment soon. In the first-in-human, single-agent, dose escalation trial of LOXO-101, 41 patients have been treated across five dose levels ranging from 50 mg once a day (Qday) to 150 mg twice a day (BID). The maximum tolerate dose (MTD) has not been reached, and the most common AEs are Grade 1 and 2 fatigue (29%), dizziness (24%) and nausea (20%). The 100 mg BID dose has been well tolerated and has been found to have adequate LOXO-101 plasma exposure to achieve inhibition of TRKA, TRKB, and TRKC at peak concentrations; therefore, 100 mg BID has been selected as the recommended phase 2 dose. In these initial 41 patients with solid tumors, seven patients had known NTRK fusion across five tumor types: sarcoma (1), papillary thyroid cancer (1), mammary analogue secretory cancer of the salivary glands (3), non-small cell lung cancer (1), and gastrointestinal stromal tumor (1). Six of these seven patients were evaluable for response evaluation and all six demonstrated a clinical response to LOXO-101. Five of the six patients achieved a confirmed partial response by RECIST v1.1, while the sixth patient exhibited a 21% tumor regression. All seven patients with NTRK fusions remain on study with no evidence of progressive disease.

In December of 2015, Loxo Oncology initiated a multi-center Phase 1 pediatric trial entitled *A Phase 1 study of the ORAL TRK Inhibitor LOXO-101 in Pediatric Patients with Advanced Solid or Primary Central Nervous System Tumors*. This study is designed to determine the safety of oral LOXO-101 including DLT, characterize the PK and identify the MTD and/or the appropriate dose of LOXO-101 for further clinical investigation, and to describe the antitumor activity of LOXO-101. LOXO-101 is administered by a weight and age adjusted dose algorithm to approximate adult exposures achieved with a 100 mg BID dose. Key eligibility criteria include: patients between 1 and 21 years old on Cycle 1 Day 1 with locally advanced or metastatic solid tumor or primary CNS tumor that has progressed, or was nonresponsive to available therapies, and for which no standard or available curative therapy exists, *OR* patients ≥ 1 month old with a diagnosis of infantile/ congenital fibrosarcoma, with a documented NTRK fusion that has progressed, or was nonresponsive to available therapies and for which no standard or available curative therapy exists. The expected sample size in this study is up to 36 patients in order to define the MTD and up to 30–60 additional patients in the dose expansion cohorts. To date, one patient has been enrolled on this clinical trial. This patient is a 16 month old with infantile fibrosarcoma with an ETV6-NTRK gene fusion. Loxo Oncology reports that at the end of Cycle 1, the patient showed a ≥90% decrease in the MRI enhancing mass from baseline and at the end of cycle 2 there was further reduction in the MRI enhancement, confirming the patient's partial response.

II. Issues Relating to the Development of LOXO-101 in Pediatrics

1. Please consider the ongoing pediatric study and provide an opinion regarding the overall study design.

2. Please consider the toxicity profile of LOXO-101 in adults and discuss whether there are unique safety concerns related to potential short and long-term toxicities from the use of LOXO-101 in pediatric patients. Also, discuss potential ways to mitigate these risks.

3. Please consider the necessity for an international collaborative study given the very rare cancers for which LOXO-101 may prove relevant.

4. Please comment on the adequacy of the current pediatric formulation and any plans for evaluation of the pediatric formulation.

5. Please comment on the clinical availability and utility of NTRK fusion identification in current pediatric oncology practice.

Second Session

PRODUCT: Entrectinib
COMPANY: Ignyta, Inc.

I. Regulatory History

Entrectinib is an orally available inhibitor of the receptor tyrosine kinases TrkA (encoded by the gene *NTRK1*), TrkB (encoded by *NTRK2*), TrkC (encoded by *NTRK3*), ROS Proto-Oncogene 1 (ROS1; encoded by the gene *ROS1*) and anaplastic lymphoma kinase (ALK; encoded by the gene *ALK*).

Gene rearrangements in each of these genes have been observed in a variety of tumor types, including non-small cell lung cancer (NSCLC), colorectal cancer (CRC), salivary gland cancer, papillary thyroid cancer, melanoma, and sarcoma. Overexpression of *NTRK2* and *ALK*, as well as *ALK* point mutations have also been observed in neuroblastoma.

Entrectinib is currently being studied in three ongoing clinical trials in adult subjects, as summarized below:

1. ALK-372-001: First-In-Human (FIH), open-label, multicenter, dose-escalation study in adult patients with advanced/metastatic solid tumors with TrkA/B/C, ROS1, or ALK molecular alterations. Ongoing in Italy.

2. RXDX-101-01 (STARTRK-1): Phase 1/2, open-label, multicenter, single-arm, dose-escalation study in adult patients with solid tumors with *NTRK1/2/3, ROS1* or *ALK* molecular alterations. Ongoing in US, South Korea and Spain.

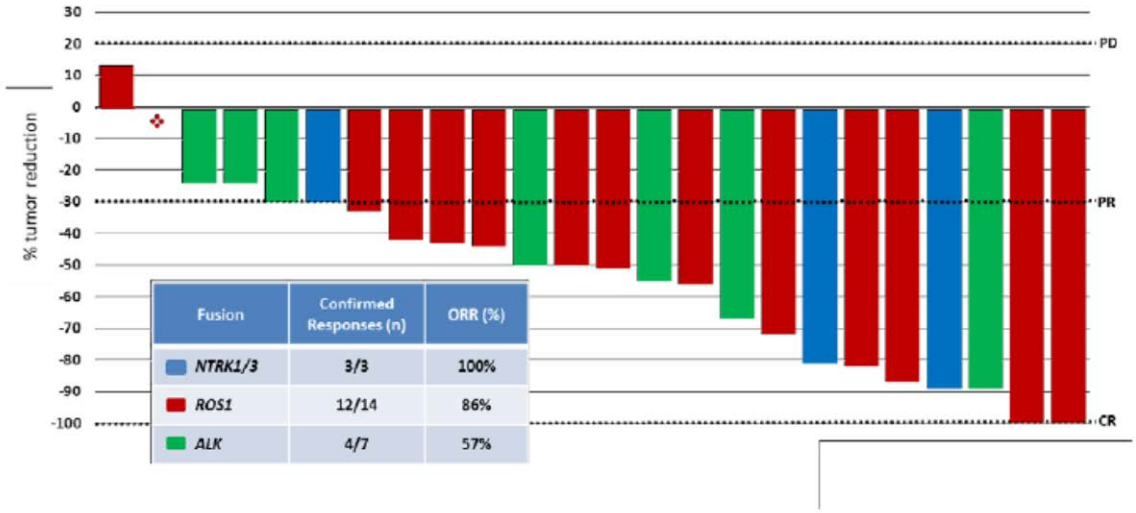
3. RXDX-101-02 (STARTRK-2): Pivotal Phase 2, global, multicenter, open-label, basket study in adult patients with advanced or metastatic solid tumors with *NTRK 1/2/3, ROS1*, or *ALK* gene rearrangements. Ongoing in US, EU, and Asia-Pacific.

As of March 7, 2016, 119 patients have been treated with entrectinib in the two Phase 1 studies (54 subjects in ALKA-372-001 and 65 patients in STARTRK-1), and the two studies are both ongoing. Based on the results of these Phase 1 studies, 400 mg/m^2 administered once daily on a fed regimen was selected as the BSA-based recommended phase 2 dose (RP2D), and 600 mg/day was selected as the fixed RP2D.

The most common (≥ 10% incidence) treatment-related, adverse events (AEs) observed across both studies were fatigue/asthenia (44%), dysgeusia (41%), paresthesia (28%), nausea (24%), myalgia (22%), diarrhea (19%), dizziness (16%), arthralgia (15%), vomiting (15%) and constipation (12%). There was no evidence of cumulative toxicity, hepatic or renal toxicity, or QT prolongation. All AEs were reversible with dose modifications.

Tumor assessments were performed at the end of Cycle 1 and every 8 weeks thereafter. Among the 24 Trk-, ROS1-, or ALK-inhibitor naïve patients with extracranial tumor harboring an *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangement who were treated with entrectinib at or above the RP2D, preliminary response rates of 100% (3/3 subjects), 86% (12/14 subjects), and 57% (4/7 subjects) were observed in the *NTRK1/2/3*, *ROS1*, and *ALK* subgroups, respectively. Overall response rate was 79% (19/24 subjects) (Figure 1).

Figure 1: Antitumor Activity in ALK and ROS1 Inhibitor-naïve Patients (n=24) with Extracranial Solid Tumors Harboring *NTRK1/2/3, ROS1* or *ALK* Gene Rearrangements



Source: Ignyta Briefing Document

The global Phase 2 STARTRK-2 study is currently enrolling in the US and is being activated in an additional 15 countries worldwide. In this study, entrectinib will be administered at a dose of 600 mg PO daily for 28-day cycles.

Ignyta recently initiated study RXDX-101-03, a 4-part, Phase 1/1b, multicenter, open-label, dose escalation and expansion study in pediatric patients with relapsed or refractory solid tumors (Part A) and primary CNS tumors (Part B). There will be two expansion cohorts for subjects with neuroblastoma (Part C) and other non-neuroblastoma, extracranial solid tumors harboring *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangements (Part D) (Figure 2). This study will enroll subjects between the ages of 2-22 with the primary objective of determining the MTD or RP2D of entrectinib in pediatric patients with extracranial solid tumors and primary CNS tumors. Secondary objectives are to describe the safety profile, to characterize the pharmacokinetics of entrectinib and to estimate the tumor response rate in all enrolled patients.

Part A: Determination of the MTD or the RP2D, PK and safety profile of entrectinib in children and adolescents with relapsed or refractory extracranial solid tumors. Entrectinib will be administered orally once daily. The starting dose will be 250 mg/m^2 and up to 4 dose levels will be evaluated. Estimated enrollment: 6-30 subjects.

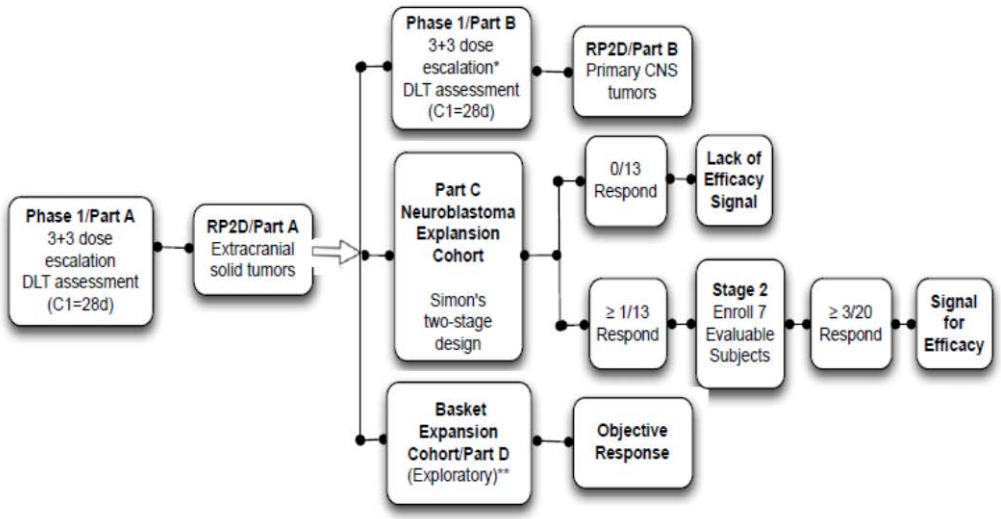
Parts B, C and D will be opened after determination of the RP2D in Part A.

Part B: Determination of the RP2D, PK and safety profile of entrectinib in children and adolescents with relapsed or refractory primary CNS tumors. Estimated enrollment: 6-15 subjects.

Part C: Evaluation of tumor response in children and adolescents with relapsed or refractory neuroblastoma receiving entrectinib at the RP2D determined in Part A (neuroblastoma expansion cohort). Up to 24 subjects will be enrolled (up to 20 evaluable subjects).

Part D: Evaluation of tumor response in children and adolescents with relapsed or refractory non-neuroblastoma, extracranial solid tumors harboring *NTRK1/2/3, ROS1*, or *ALK* gene rearrangements (basket expansion cohort). Up to 12 subjects will be enrolled (up to 10 evaluable subjects).

Figure 2: Schema for Study RXDX-101-03



RP2D=recommended phase 2 dose, DLT=dose limiting toxicity
*Starting dose level= RP2D/A-1 dose level
**Presence of *NTRK1/2/3, ROS1*, or *ALK* gene rearrangement documented by a CLIA lab.

Source: Ignyta Briefing Document

A pediatric drug product formulation comprising granules meant to be sprinkled over soft food ("sprinkle formulation") that can be swallowed without chewing is being progressed to support the initial clinical development plan in children. Ignyta plans to test the sprinkle formulation in healthy adults in order to verify the *in vivo* performance (PK exposure) before using it in pediatric patients.

This study is currently enrolling at 4 sites in the US. No data have been disclosed to date. Ignyta proposes that this trial can be used as the basis for a Written Request from the FDA.

II. Issues Relating to the Development of Entrectinib in Pediatrics

1. Please consider whether NTRK1 and 2 and ALK overexpression provides an appropriate biological rationale for the proposed target tumors. Please address the role of ROS1 inhibition in pediatric tumors.

2. Please comment on the clinical availability and feasibility of *NTRK1/2/3* and *ROS1* evaluation in current pediatric oncology practice.

3. Please consider the ongoing pediatric study and discuss the overall study design.

4. Please consider the toxicity profile of entrectinib in adults and discuss whether there are unique safety concerns related to potential short and long-term toxicities from the use of entrectinib in pediatric patients. Also discuss potential ways to mitigate these risks.

5. Please address whether evaluation of this drug in pediatrics would require international collaboration.

6. Please comment on the adequacy of the current pediatric formulation and any future plans for the pediatric formulation.