FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE PEDIATRIC SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE (pedsODAC)

Morning Session

Wednesday, June 29, 2016

8:00 a.m. to 11:08 a.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Subcommittee

DR. PAPPO: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices, if you have not done already.

I would also like to identify the FDA press contact, Angela Stark. If you are present, please stand.

I would now like to ask the members, consultants, FDA panel, and DFO to go around the table and state their name into the record.

DR. MORROW: P.K. Morrow. I am a medical oncologist employed by Amgen.

DR. WARREN: Kathy Warren, pediatric neuro-oncology, NCI.

DR. RAETZ: Elizabeth Raetz, pediatric oncology, University of Utah.

DR. DUNKEL: Ira Dunkel, pediatric oncology, Memorial Sloan Kettering.

MS. MCMILLAN: Gigi McMillan, patient representative.

MS. HAYLOCK: Pamela Haylock, oncology nurse and consumer representative.

DR. ARMSTRONG: Deborah Armstrong, medical oncologist and chair of adult ODAC.

DR. PAPPO: Alberto Pappo, pediatric oncologist, St. Jude Hospital in Memphis and chair of the pediatric ODAC.

DR. TESH: Lauren Tesh, designated federal officer, peds ODAC.

DR. NEVILLE: Kathleen Neville, pediatric oncologist and clinical pharmacologist at Arkansas Children's Hospital.

DR. WEIGEL: Brenda Weigel, pediatric oncology, University of Minnesota.

DR. MacDONALD: Tobey MacDonald, pediatric oncologist, Emory University.

DR. GLADE BENDER: Julia Glade Bender, pediatric oncology, Columbia University.

DR. SEIBEL: Nita Seibel, pediatric oncology, NCI.

DR. OSGOOD: Christy Osgood, FDA Division of Oncology and Hematology Products.

DR. ERSHLER: Rachel Ershler, pediatric oncologist, FDA, Division of Oncology and Hematology Products.

DR. REAMAN: Gregory Reaman, associate director, Office of Hematology and Oncology Products.

DR. PAPPO: Thank you very much.

Dr. Brown is just walking in. If you don't mind just introducing yourself for the record, we will wait for you.

DR. BROWN: Pat Brown, pediatric oncologist from Johns Hopkins. Tardy.

(Laughter.)

DR. PAPPO: Thank you.

We will now proceed with opening remarks from Dr. Greg Reaman.

FDA Introductory Remarks/Presentation

DR. REAMAN: I just want to welcome everybody back again today. Thank you for coming.

Just to remind everyone, the purpose of

these meetings is really to provide some input, advice to the agency on new promising agents, novel agents for potential pediatric indications that would help inform us in the formulation and potentially in issuing a written request.

There was a comment made yesterday that this wasn't early, the pediatric studies that were being done with a specific product, but I'd like to point out that I think the discussions that we'll have this morning contradict that fact and that pediatric studies are being performed. Pediatric development plans are being considered in products that aren't yet approved.

We are really trying to expedite and facilitate as early as we can the consideration of pediatric development, when it is appropriate and when the products are relevant.

The other thing to focus on, I think, today is that yesterday I mentioned that the Pediatric Research Equity Act that mandates pediatric evaluation or assessment of new molecular entities or approved entities when there is a new dosage

form or a new indication is exempt when there is orphan designation.

In the few situations where the cancers of adults for which products are developed occur relatively infrequently in children, like Hodgkin's disease, some forms of AML, the requirement for studies under PREA are exempt, because those conditions or indications have orphan designation. Again, we are caught because we're talking about products here that will be developed or are being developed to address unmet medical needs in rare cancers -- rare cancers, period -- very rare cancers in children.

Again, I think these are important discussions and appreciate your insight and input there. Thank you.

DR. PAPPO: Thank you very much.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that

individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

We will now proceed to topic 1, Loxo-101 from Loxo Oncology, Incorporated. Dr. Lauren Tesh

will read the conflict of interest statement for this session.

Conflict of Interest Statement

DR. TESH: The Food and Drug Administration is convening today's meeting of the pediatric subcommittee of the oncology drugs advisory committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in

compliance with federal ethics and conflict of interest laws under 18 U.S.C. Section 208. Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to effect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing,

patents and royalties, and primary employment.

This session's agenda involves information to gauge investigator interest in exploring potential pediatric development plans for five chemical entities 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 product under consideration for this session is Loxo-101, presentation by Loxo Oncology, Inc. This is a particular matters meeting during which specific matters related to Loxo Oncology's product will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, a conflict of

interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Pappo. Dr. Pappo's waiver involves his employer's current study of Loxo interest and funded by Loxo Oncology which is anticipated to be between $50,000 and $100,000 per year in funding.

The waiver allows this individual to participate fully in today's deliberation. FDA's reason for issuing the waivers are described in the waiver documents, which are posted at the FDA's website. Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland 20857, or requests may be sent via fax to 301-827-9267.

We would like to disclose that Dr. DuBois has self-recused himself from participating in this session of the meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. P.K. Morrow is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Morrow's role at this meeting is to represent industry in general and not any particular company. Dr. Morrow is employed by Amgen.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all participants to advise the committee of any financial relationships that they may have with the firm at issue.

Thank you.

DR. PAPPO: Thank you.

Both the FDA and the public believe in a

transparent process for information gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the sponsor's

presentation.

Industry Presentation - Josh Bilenker

DR. BILENKER: Good morning. I am Josh Bilenker, a medical oncologist and CEO of Loxo Oncology. Thank you for this invitation. It is an honor to present to this committee on behalf of the Loxo-101 development team.

In the next 20 minutes, I will be discussing Loxo-101, a selective inhibitor of the TRK family of kinases. I will highlight some of Loxo-101's key attributes and provide an overview of our reported clinical data. I will also review our development thinking around TRK fusions with an emphasis on pediatric cancers.

Given the rarity and diversity of TRK fusion cancers, it is our conclusion that comprehensive molecular testing is the best approach to realizing the full potential of this molecular target. It is our hope that the discussion this morning inspires clinicians, investigators, lab directors, diagnostics companies, and payers to overcome the institutional barriers that today limit access to

comprehensive testing for children with advanced cancer.

Today we will be talking about TRK as a cancer target, but neurobiologists have been studying TRK for decades. The TRKA, B, and C receptors are encoded by the genes NTRK1, 2, and 3. They sit at the cell surface and bind neurotrophins, such as nerve growth factor and brain-derived neurotrophic factor. When activated, TRK receptors signal through familiar downstream pathways, such as the MAP kinase and PI3 kinase pathways.

TRK signaling plays an important role in embryonic development in the formation of the central and peripheral nervous systems. In postnatal physiology, the TRK family regulates pain, movement, memory, and proprioception.

In 1986, the first oncogenic fusion was described in a colorectal cancer cell line. Since then, TRK fusions have been described across many different cancer types. These fusions lead to a chimeric TRK protein that is constitutively

expressed and capable of ligand independence signaling. Conceptually, then, TRK is similar to other oncogenic fusions, such as BCR-ABL and EML4-ALK.

Given the role of TRK signaling in pain and cancer, our development partner, Array BioPharma, used x-ray crystallography to identify highly selective inhibitors of TRKA, B, and C. Loxo-101, our development candidate, came from these efforts.

Loxo-101 is highly selective relative to other kinases and spares other problematic off-targets, such as the hERG channel. In the kinome dendrogram, shown to the right, one can see that TRK is structurally similar to familiar targets, such as ALK, ROS1, DDL1, and FLT3. Dialing out these and other off-target kinases required a dedicated medicinal chemistry effort.

Loxo-101 was chosen for clinical development because of its clean profile and other factors to be discussed shortly.

Loxo-101 has proven to be a potent inhibitor of TRKA, B, and C in both enzyme and cell-based

assays. In the top left panel, we show that Loxo-101 inhibits NTRK1 and NTRK3 fusion cell lines at low nanomolar concentrations. We also show, in the top right panel, that Loxo-101 has no activity against other cancer cell lines, including ALK, ROS1, and EGFR lines. Together, these data are consistent with the selectivity profile discussed in the previous slide.

In the bottom panels, we show data from three in vivo tumor xenograft experiments. The Cuto3.29 and the MO-91 models exhibit frank tumor regressions, while the immortalized KM12 model, which is part of the standard NCI 60-cell line panel, exhibits tumor growth inhibition.

In summary, preclinical data suggested that clinically achievable exposures of Loxo-101 could deliver single agent tumor responses in patients with TRK fusion cancers.

The Loxo-101 development program includes both adults and children and is focused on TRK fusion cancers. Our phase 1 trials accommodate patients unselected for TRK fusions, as well as

patients specifically referred for enrollment because of a known genetic diagnosis.

Here, we list the publicly disclosed enrollment of TRK fusion patients across the Loxo-101 program. In October 2015, we launched the phase 2 basket study, called the NAVIGATE trial, which is restricted to patients with TRK fusions. This trial was initially designed for patients 18 and older, but after discussions with the agency, we recently amended the protocol to include patients as young as 12.

Loxo-101 was selected as the reference TRK inhibitor for the NCI-MATCH and Pediatric MATCH trials, though these trial arms have not yet opened.

In the adult phase 1 study, Loxo-101 was generally well tolerated. Doses have ranged from 50 milligrams daily to 150 milligrams twice daily. A maximum tolerated dose has not yet been established. A 100 milligrams twice daily is the recommended phase 2 dose based on modeling of target coverage, observed clinical efficacy, and a

favorable tolerability profile.

There have been very few grade 3 or 4 adverse events, regardless of attribution, with most adverse events being grade 1 or 2. Adverse event interpretation is confounded in the phase 1 setting by patients without TRK fusions who were enrolled on the trial, but progressed very quickly.

We will have a better understanding of the tolerability profile of 101 in the phase 2 setting, where TRK fusion patients are expected to respond and hopefully remain on study for a long time. Given our early discussions of the neurobiology of TRK, we should note that we have seen a few cases of transient grade 1 and 2 dizziness in the phase 1 trial. Temporally, this side effect may be related to Cmax, though we have also noted a possible association with prior head and neck surgery and radiation.

At the phase 2 dose of 100 milligrams BID, Loxo-101 has demonstrated consistent and durable efficacy in patients with TRK fusions. Here, we present the 6 TRK fusion patients from the adult

phase 1 trial, evaluable for response as of the date of cutoff. These 6 patients encompass 5 discrete pathologic diagnoses, including non-small cell lung cancer, a salivary gland cancer known as MASC, GI stromal tumor, papillary thyroid cancer, and an undifferentiated soft tissue sarcoma.

In this waterfall plot, we show best response by RECIST. You will see that 5 of 6 patients meet a confirmed partial response definition. Four of these patients were treated at the phase 2 dose of 100 milligrams BID, one patient was treated above this dose at 150 milligrams BID, and one patient was treated below this dose at 100 milligrams daily.

Below each bar is the number of monthly cycles the patient is on study. All patients remain in response, with the longest followed out to 14 months.

Let's take a look now at the longest responding patient, shown on the far right. This is a 41-year-old mother of three who had a metastatic soft tissue sarcoma with significant

disease burden. She had progressed through combination chemotherapy and other investigational therapies.

Upon study entry, she had a declining performance status and required supplemental oxygen. As you can see, her lung lesions have regressed dramatically and quickly, and her response has deepened over time.

This case report was first written about in the Journal of Cancer Discovery.

At 100 milligrams BID, Loxo-101 delivers the systemic free exposure, shown here in purple, and the estimated free brain exposure, shown in blue. The horizontal lines depict conservative free fraction concentrations of Loxo-101 required to deliver 90 percent and 50 percent inhibition of TRK signaling.

At the phase 2 dose, Loxo-101 provides sustained IC90 coverage peripherally and pulsatile IC50 coverage in the brain. Perhaps this pulsatile exposure in the CNS explains the favorable tolerability profile and lack of MTD identification

in the phase 1 thus far.

We deliberately designed Loxo-101 to meet this plasma-to-brain profile because of the normal TRK expression and function story I described previously regarding the central nervous system. We would be happy to elaborate on this choice during the discussion following our presentation.

Encouraging results from the phase 1 trial led to the launch of this phase 2 basket trial in October 2015. We call it the NAVIGATE trial, and like all basket studies, it is designed to include patients according to a genetic diagnosis, not an anatomic one.

Patients receive 100 milligrams twice daily and are treated until progression. We do pre-specify certain subgroups for separate review and futility assessment. This design allows for the possibility that there could be context-dependent differences in TRK fusion biology. We include a separate group for CNS tumors, which are measured for response by standard RANO criteria.

This trial is underway and enrolling well.

In the conduct of this trial, we have learned that clinical sites with an institutional commitment to comprehensive testing are able to identify TRK fusion patients.

Our thoughts regarding pediatric development have been informed by this experience. Importantly, we have confirmed what the literature predicted, that TRK fusion cancers are diverse and that an unusually high number of fusion partners have been described for TRK, at least 46 in the literature, in addition to many other novel partners we have identified in our clinical trials.

Perhaps more importantly, we have enrolled patients with well over 10 discrete anatomic diagnoses. Since we are seeing consistent activity for Loxo-101 regardless of fusion partner or primary diagnosis, our protocols are designed to accommodate any patient of any age with any diagnosis who has a documented TRK fusion cancer.

While the full disease burden associated with TRK fusions in children is unknown, there are several disease settings where TRK fusions have

been widely reported. These 6 pediatric cancers are known to harbor TRK fusions in a meaningful proportion of patients.

Some of these represent clear development footholds for Loxo-101. For example, in papillary thyroid cancer, as many as a quarter of patients under the age of 18 may have disease attributable to a TRK fusion. Pediatric sarcomas, including but not limited to infantile fibrosarcoma, also have TRK fusions.

In our briefing book, we consider where there might be unmet needs in the management of some of these cancers. Let's consider infantile fibrosarcoma in more detail. In the last decade, we have learned that TRK fusions are pathognomonic for this disease, the most common soft tissue sarcoma in children younger than the age of one.

As you know, this rare congenital cancer is often cured by surgical resection and chemotherapy. It presents in the extremities or in the head of neck and usually follows a benign course. However, a subset of patients requires limb-sacrificing

surgery or disfiguring resections in the pursuit of negative surgical margins. Some patients develop refractory, locally advanced, or systemic disease. There is need, we believe, for a highly active, well-tolerated systemic therapy in these settings.

Here's a recent case from our phase 1 pediatric trial. We were contacted by a physician caring for a 16-month-old with infantile fibrosarcoma. The patient had already been through multiple surgical resections and combination chemotherapy regimens. She had residual disease involving the base of the skull which was progressing.

She received Loxo-101 formulated as a liquid at a dose estimated to approximate the 100 milligram BID dose in adults. She experienced a 90 percent reduction in tumor volume by MRI on the first scan at 30 days. This response was confirmed 30 days later, meeting the definition of a confirmed partial response.

The patient has had no evidence of drug-related toxicity and is now again achieving

developmental milestones. Her case was recently published in the Journal of Pediatric Blood and Cancer.

As the safety and efficacy of Loxo-101 are better understood, there may be an opportunity to reduce the role of chemotherapy or high morbidity surgical procedures in the setting of infantile fibrosarcoma.

Another pediatric cancer worth mentioning is neuroblastoma. There is a 20-year history of literature connecting TRK to neuroblastoma prognosis. Full-length TRKA and C expression are correlated with favorable prognosis, but TRKB expression is correlated with an unfavorable one. It is not clear what these contradictory prognostic signals say about the clinical potential of a pan-TRK inhibitor that antagonizes TRKA, B, and C equally.

Preclinical models suggest that TRK inhibitors can inhibit tumor growth, but do not cause single agent regressions. An older study employing a drug called multikinase inhibitor with

anti-TRK activity, reported two lestaurtinib, a objective responses in a highly refractory patient group.

In the face of complicated biology, a drug as selective as Loxo-101 is a pure test of the TRK hypothesis in neuroblastoma. We expect to enroll neuroblastoma patients in our ongoing phase 1 pediatric trial.

Loxo-101 is a soluble stable drug that allows for many formulation options. We have developed a taste-masked liquid formulation. For the pediatric phase 1 trial, we conducted preclinical bridging studies that showed comparable release and exposure kinetics to a powder in capsule formulation which we are developing in adults.

We are currently accruing to a phase 1 pediatric study called the SCOUT trial, which includes patients 1 to 21 years of age or younger if they have infantile fibrosarcoma or congenital nephroma.

A dosing nomogram based on SimCyp modeling

informs dose selection. Though unlike a typical dose-finding trial, we are targeting the adult equivalent, 100 milligrams BID, exposure from the first dose cohort. Intrasubject dose escalation is allowed based on real-time PK assessment.

While all advanced cancer patients are eligible, most investigators are choosing to enroll patients with lab-confirmed TRK alterations or diseases where TRK biology may be relevant.

It is our plan to expand this protocol to focus on biologically-defined cohorts, with an emphasis on TRK fusions. Examples of cohorts we are considering are shown to the right, which include infantile fibrosarcoma, other TRK fusion cancers, non-fusion TRK genetic alteration cancers, and neuroblastoma.

The rarity of TRK fusions in pediatric cancer raises many of the same questions we have tackled in our adult development. We are thinking carefully about how to build a regulatory package to support Loxo-101 in pediatrics.

For certain tumors that impact both children

and adults, such as thyroid cancer and sarcoma, there may be an opportunity to analyze data across more than one trial. Based on the activity we have already seen, we would like to modify our pediatric phase 1 trial to include expansion cohorts that address key TRK biology and clinical questions relevant to pediatric patients. This streamlined trial design will allow us to leverage the trial infrastructure already in place for this drug.

Finally, the selection of Loxo-101 to be part of the Pediatric MATCH trial is an opportunity to confirm activity signals and safety over time.

TRK fusion cancers may be the first truly genetically-defined cancers where anatomic site of origin is a minor variable in drug development and clinical management. Because TRK fusion cancers are rare and occur in diverse clinical settings, it doesn't make sense to develop a standalone diagnostic test that exhausts precious tumor material to answer one or just a few questions.

Comprehensive genomic profiling offers the ability to exploit the full potential of Loxo-101

and other targeted therapies. Though there are technical issues around gene fusion testing that require special attention, utilizing RNA as the testing substrate solves many.

It takes many stakeholders working together, clinicians, investigators, lab directors, diagnostics companies, and payers, to bring the clinical management of advanced pediatric patients to the edge of scientific knowledge. Hopefully, exciting clinical results such as these will encourage better and more frequent testing for TRK fusions and the growing list of other actionable targets.

In conclusion, I hope you have heard today that TRK fusions have joined the canon of other dominant oncogenic activating genetic alterations in cancer and that Loxo-101 was rationally designed for its potency and selectivity. Our early clinical experience in pediatrics appears consistent with our adult experience; namely, that a TRK fusion predicts sensitivity to Loxo-101 regardless of primary diagnosis or fusion partner.

Finally, I hope you heard that we are committed to the responsible and rapid development of Loxo-101 in pediatric cancer.

Thank you again for allowing us to present here today.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you very much.

We will now take clarifying questions for the sponsor. Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter.

Dr. Warren?

DR. WARREN: Hi. Kathy Warren from the National Cancer Institute.

Can you go ahead and allude on the balance between CNS penetration and potential efficacy for CNS tumors and CNS toxicity? Is the exposure for toxicity less or higher than what we would need for exposure for anti-tumor effects?

DR. BILENKER: Thank you for the question.

I will walk you through a few more slides of our thinking on the topic. There is a long

literature linking TRK to normal CNS development. As shown on this slide, TRKA knockout mice have neuron loss in the dorsal root ganglia. TRKB causes effects on the trigeminal ganglia, also dorsal root ganglia on motor neurons, and TRKC affects large myelinated axons.

Next slide.

There are also two inherited kinaseopathies reported in the literature. There is a congenital insensitivity to pain with anhidrosis syndrome, which leads to self-mutilation and trauma in affected individuals. There is also even a case report of a TRKB mutation which caused developmental delay, impairment of short-term memory, impaired nociception, hyperphagia and obesity. These are developmental arguments for being concerned about the TRK pathway in any TRK inhibitor development program.

Next slide.

There were also clinical lines of evidence suggesting that TRK inhibition in the brain could cause deleterious effects in people. There are

clinical studies of two compounds from Nerviano Medical Sciences. The first study by the call letters listed on this slide was reported from a phase 1 setting where two dose schedules were explored, a 7-day on, 7-day off schedule, a 4-day on, 3-day off schedule with one week off rest, as well. Ataxia and tremor were dose limiting in these settings for that drug.

Another sponsor presenting today will discuss how neurotoxicity affected their selection of clinical dose.

We saw the issue of CNS inhibition in the brain of TRK as a real perhaps limiting issue for peripheral exposures and that pulsatile exposures might be a better option moving forward. That led us to conduct some preclinical experiments, which I will show you on the next slide.

With particular focus driven from the literature that TRKB is important for normal movement, memory, and activity, we looked at rats in two proprietary models of CNS behavior. One was an ataxia score, where we charted and which I am

showing here, and I will explain in a moment. The second was we conducted so-called rotarod experiments, where rats were asked to, basically, after training, balance on a spinning wheel, kind of like a log roller which you would see on TV.

I will focus here on the ataxia score data we showed, and we saw a clear PK/PD effect with regard to ataxia and behavioral problems in animals. In other words, if you look at the top panel A, you will see that the above two lines, those two doses, 100 and 300 milligrams, are above the IC90 levels causing TRK inhibition in the brain. The lower dose, however, flirts above the IC50 line, but doesn't approach IC90 levels.

When you look to the panel to the right, we are actually mapping ataxia scores over time. Interestingly, we see a delayed onset of ataxia. They come on between 10 and 14 days of exposure.

The red line is our highest dose, and you will notice that ataxia does not reverse in that setting. At the lower dose of 30, in purple, there is reversibility, and it was less severe to begin

with, and that's the dose that correlates with IC50 coverage.

To us, drawing from these three lines of evidence, literature, previous clinical studies of other TRK inhibitors, as well as our own proprietary work, that suggested that a pulsatile profile of transient brain exposure would be best.

Next slide.

Here is the most direct answer to your question, where we are modeling target coverage, where we integrate the potency of the drug, its protein binding, which accommodates, obviously, its free fraction. You can see that our phase 2 adult dose of 100 BID delivers sustained IC90 coverage peripherally, in purple, whereas in the brain, that same dose delivers transient or pulsatile IC50 coverage in the brain.

There is ample literature from adult settings in cancer where IC50 coverage in the brain, such as in the EGFR space or ALK space, can deliver objective tumor regressions.

Next slide.

The overall disease burden we are seeing for TRK fusion cancers, with, obviously, the notable exception of primary CNS tumors, the overall disease burden of cancers that go to the brain harboring TRK is very low, in our experience. Here, we are showing you really the only case we have, showing you how low it is.

However, this patient did have brain metastases at baseline, some midline abnormalities, as well as some in the occipital region. Although his disease burden in the CNS is low, we were heartened to see an improvement or a regression of these lesions over time, which correlate to his improving lung burden, as well.

DR. PAPPO: Thank you.

Does that answer your question?

DR. WARREN: Yes.

DR. PAPPO: Thank you.

Dr. Weigel?

DR. WEIGEL: Thank you. Brenda Weigel.

I have a few questions. One was similar along those lines, and I congratulate you for

really focusing on pediatric development and for starting your pediatric phase 1 at what we think will be a meaningful full dose, the equivalent of the adult recommended dose.

One of the challenges, I think, following up a little bit on the questioning now, is that according to the information provided, you have a dose escalation plan that goes to about three times what is the current recommended phase 2 dose for adults, and you haven't reached an MTD in adults, at least as presented and as I understand.

How are you making that decision to escalate purely on toxicity if you think the optimal pharmacokinetics are around this dose? You alluded to that you are allowing intrapatient dose escalation. How is that decision-making being played into the data that was just presented?

DR. BILENKER: Fortunately, we will have the help from our investigators to make the final decision of dose in the phase 1 setting. I will just remind you -- slide up -- that in the adult setting, we are seeing consistent efficacy at a

range of doses which do include and straddle our recommended phase 2 dose.

Next slide.

There are some subtleties in our design of the phase 1, which if you allow, I will walk through briefly here.

Again, this is a phase 1 multicenter, open label study. It is a rolling six design. Loxo-101 is delivered BID. Based on SimCyp modeling, we came up with a dosing nomogram that incorporates body surface area, as well as the age of the patient, obviously reflecting CYP3 ontogeny in those different settings. We are using that to select a given patient's dose by cohort.

It is a little confusing and subtle. If you look at our dose cohort definitions, which are expressed in milligram-based doses, that is really just the target dose. That allows us to pick a different spot.

Two slides back up.

Here is an example for dose cohort 1 of how the dosing nomogram looks. The nomogram slide,

slide up.

In cohort 1, for example, with the BSA known, with the age of the patient known, it allows us to pick the spot on the grid. You can think of our so-called dose escalations effectively going down and to the right over time, though they are called by milligram names.

Since we have ample PK assessment in this trial setting, our investigators are getting real-time PK information back in real-time, and they can adjust the patient up at their discretion towards the range of exposures we have seen at the 100 BID dose.

The protocol is written today deliberately for flexibility. As we get more dose experience, we will learn, A, how close we are with our first guess to a desired pediatric concentration. Secondly, we will be able to elucidate whether there are unique safety issues in children and whether the tolerances are the same or not. But with the advice from our safety committee and investigators, our plan is to go up high.

I will show you one other idea to consider.

Next slide.

Here is a PK curve from our adult experience, to the right. To the left, we are showing dose proportional Cmaxes, and to the right, we are showing their impact on AUC. We are getting micromolar exposures at Cmax, and this is a log scale. So some of the differences between dose levels are blunted in the visual impact.

However, you will see that with increasing doses, we have an impact on Cmax first, not surprisingly, but the shapes of the curves and the sustained coverage of IC90 and 50 are generally similar as we are moving up modestly by dose. Because we were able to start with biologically relevant doses from the beginning of this design based on just our therapeutic window in animal IND enabling studies, we were able to get onto this curve pretty quickly in the adult phase 1 setting.

This PK model, to us, also has us scratching our head a little bit, how much efficacy are we really leaving on the table or gaining, I should

say, as we go up 50, 100 milligrams at a time. But we are willing, certainly, to keep going.

If it seems that patients with CNS tumors require more dose or it seems that pediatric patients tolerate the drug unusually well, I think we are all in the camp of more is better. And we are going to again defer to our investigators for help with this PK-directed choice of dose.

DR. WEIGEL: Thank you. Because I think it is a real challenge given that you haven't reached maximally tolerated dose and you may not and you may not in your adults actually choose to do that. It is how do we define, particularly in the CNS space, the optimal dose in children.

As you allude to, we may need to push the dose higher to get that optimal exposure in the CNS. I think it is a real challenge.

A follow-up question. It sounds as if you are really designing this as a real-time PK assessment to optimize a target range and that target range seems to yet be completely defined based on the adult data. There are two moving

parts.

Am I understanding that correctly or have I overstated? In the adults, you have a target range that you think is likely for the adult tumors. We are not sure if that is necessarily the optimal target range, but it was a good starting point, and I congratulate you for that, for the pediatric tumors. But we may need a different dose potentially in children for CNS optimization, and defining that dose if we are not actually going to see a maximally tolerated dose due to classic toxicity assessments.

I guess that is the challenge of the decision-making. I am not saying it is easy, and I am not saying there is a great answer to that. I am saying it is a real challenge, because it is a little bit of a moving target.

You don't need to comment or answer, because I am not sure there's a great answer to that.

The other question I have, it alludes again to the CNS toxicity. You alluded to enhanced toxicity in combination with radiation therapy.

Can you expand on that a little, what you are seeing, what the potential toxicities are there, and is that a space that needs to be explored a little bit more in combination, especially for CNS patients?

DR. BILENKER: It is so hard to parse relatedness to toxicity in a phase 1 setting when patients have so many inter-occurring illnesses. As I mentioned, in the phase 1 setting, many of our patients were unselected for TRK fusions. Most of those patients progressed within two cycles. Their disease progression was captured in our adverse event table.

We have noticed in a couple of dizziness cases, those patients just happened to have had extensive head and neck surgery. You remember this disease entity that we discussed on the waterfall plot, masked tumors, it's mammary analogue secretory cancer of the salivary glands. It is fairly new. It is a mouthful, and some pathologist maybe should have named it after himself instead.

(Laughter.)

DR. BILENKER: But obviously, many of these patients have prior head and neck surgery and radiation, and we just noticed that some of these patients seem a little more sensitive. They even come on the study with fragility, by clinician report, of having other kinds of CNS-type symptoms prior, and maybe this drug exacerbates those.

There is literature, as you know, where there is compromise of the blood-brain barrier in the setting of radiation. It is possible that we are getting more into the brain for longer periods of time and causing and seeing more dizziness.

But I can tell you that we are really interested in the question, especially in peds.

Slide up.

In our electronic case report form, we have built this dedicated neurologic questionnaire, where we are covering cognitive disturbances, ataxia, dizziness, memory impairment, parathesias, et cetera. We are really encouraging our investigators to look out, be careful, be on guard, given the issues of detecting tox in children who

are not the best historians for this sometimes.

We are really concerned about the issue, and our case report form will capture it.

DR. PAPPO: Thank you.

Dr. Seibel?

DR. SEIBEL: Thank you for your presentation. And do you have any data about developmental resistance to Loxo-101?

DR. BILENKER: We do. Very interesting story. Slide up, please.

Acquired resistance, unfortunately, is a common fact in development of targeted therapies. Fortunately, in the last several years, we have a better structure-based understanding of why they occur.

As of this presentation, Loxo-101, we have seen no progressors among responders. We have not seen this yet clinically, but there are two case reports of patients who progressed on entrectinib. One patient developed a G595R mutation, and another patient developed a G623 mutation. Both these case reports are published, by the way.

Both of these are occurring in the so-called solvent front of the ATP binding site of the kinase domain. In brown, I am showing you a scaffold of our drug, Loxo-101, and in green, you will see that 595 arrow where the solvent from it is. You can imagine if you replace that position with a bulky amino acid, the binding kinetics of Loxo-101 are likely to be different.

Towards the right of the picture is where the gatekeeper mutations occur, and there are others. Interestingly, 595 and 623 are exact paralogues of the ALK 1202R mutation and the ROS1-2032R mutation. If you line up the amino acid chains for these different kinases, ALK, ROS and TRK, and you look at the amino acid positions, where they overlay in space, they are exactly paralogous.

It is pretty interesting to see two, one patient in Italy, one patient in New York City, not to mention lining up with prior descriptions in ALK and ROS. That presented a company like ours with a conundrum. We are doing all this work to find

these rare TRK fusion patients. If and when they progress, we want to be ready.

We did some work preclinically, which we published in the AACR, slide up, with the Doebele lab in Colorado, where we did directed mutagenesis experiments, where it is possible to, in the lab, pressure a system and drive resistance to your drug. Then you characterize where those amino acid changes occur. We can provide this reference subsequently.

What you basically see is when one of these amino acid changes occur, this is a bit of an artificial environment, and it doesn't always predict clinical effect, doesn't always predict the clinical mechanisms of resistance, but it can. In this case, it did.

That led us to then go back to our chemistry library -- next slide -- where we had a compound sitting around that was chemically diverse from Loxo-101. It is called Loxo-195, and it is a highly potent nanomolar, very selective drug, very similar in profile to Loxo-101 in terms of its

selectivity, but again, structurally distinct.

It is active against all the reported acquired resistance mutations that have been reported clinically, as well as the relevant preclinical identifiers. This drug, we are accelerating its development to tuck it in behind Loxo-101. It is poised to enter the clinic in 2017.

Our goal, again, is to be ready. In previous targets, EGFR, whether it is T790M or ALK, like I showed you, with 1202, there is often a multiyear gap or delay between first gen and second gen, and the patients who develop those mechanisms of resistance, unfortunately, don't have a therapeutic option waiting. Our goal is again to tuck this right in behind and be ready in the case that the patients progress because of a point mutation that confers binding resistance to Loxo-101. Stay tuned on this, but we are really trying to follow this literature closely.

DR. SEIBEL: You said that you haven't had any patients who responded who have gone on to

progress or develop resistance; is that correct?

DR. BILENKER: That is correct.

DR. SEIBEL: Have any patients who have responded come off the drug?

DR. BILENKER: I am really going to limit my comments today to disclosed patient information, but I can say that the phase 2 experience we are seeing is very consistent with our phase 1 experience. What we are seeing out in the field is we are seeing a variety of patients with a variety of health status, as well as a variety of testing platforms with the TRK fusion.

We are studying all those patients very carefully to make sure indeed they are TRK fusion patients primarily. But again, the drug is behaving very well, and please stay tuned. We are running a registration-enabling trial potentially with our phase 2 basket study, so we want to be very careful about how we disclose data.

DR. SEIBEL: Then in the case you showed of the 16-month-old, the patient had a response within 30 days. Is that the usual pattern, or is it a

more extended response? Can you give us more information about the response timing?

DR. BILENKER: Yes. I can give you a better sense of the temporal response. Why don't we just walk through a couple of cases where I can show you some freeze frames where you will see the early response and you will see a deepening.

Slide up.

We talked about the sarcoma patient. Within three days of her first dose, she felt markedly better. By her day 8 PK draw, she was bounding up the stairs in Colorado at altitude without oxygen. Something had clearly changed for this patient within the first week of dosing, and her lung scan, we don't show -- she had a 30-day scan, because everybody was so excited, but I'll show you here her cycle 3 scan. Then you see even a deepening of response over time.

We see a very rapid and immediate improvement in symptoms, but we do see improved radiographic deepening over time.

Next slide.

Here is just another patient who presented with a GIST tumor. You can see his PET scan on the top panel, a high disease burden in the liver and abdomen, large liver lesion. His abdominal pain went away. He was mowing his lawn within the first couple of weeks of dosing. Something also had clearly changed for him clinically, and his CAT scans, I think, support that time course.

Next slide, please.

Here is a patient who had rapid reduction in cough symptoms, deepening response over time.

Next slide.

The disease burden in this patient is slightly lower, but you can see at cycle 3, they are shrinking. Then the next cycle, even better.

Then the next slide is a 33-year-old who had miliary disease in the lung, these smaller lesions, had a lot of cough and shortness of breath. Within a month or two of dosing, he decided to start training for a marathon. He was a runner before.

The clinical symptomatology improves very dramatically. The earliest scans we have are from

30 days, and those all show shrinkage. It is exciting to work with this drug in the clinic.

DR. PAPPO: Thank you.

Ms. McMillan?

MS. MCMILLAN: Excuse to you.

You mentioned that one of the risks about this is identifying patients me for asking a question with my back, and you promote comprehensive genomic profiling for the pediatric patients. Can you talk about the relation between the potential success of this agent and the requirement for a comprehensive genetic profiling on a large-scale basis?

DR. BILENKER: I am glad you asked because we really feel like this is the issue for this program. It is a highly active drug, and it is just about finding patients.

The patients we have enrolled, it almost at times feels like happenstance, but the ability to have gotten the patient came from tumor tissue that happened to be sent to a central reference lab with good fidelity or the patient pushed for it.

Let me just, if I may, just take a few moments to think about some of the testing issues with you. They are not trivial. They are not trivial technically, and they are not trivial from an implementation standpoint, much less payer issues and the rest.

If you will indulge, I will just take a few moments and walk through a few slides on testing. Slide up.

The perfect test is minimally invasive; comprehensive; sensitive and specific; requires straightforward specimen handling; doesn't require a master's degree, in other words, in the lab; low cost, but well reimbursed; easily interpreted; and, affects clinical decision-making. That's the perfect test. We don't have that at all.

What we do have -- next slide -- is this grid of four different methods that have the ability, at least in theory, to detect a TRK fusion. We have next-gen sequencing. We have RT-PCR. We have FISH and IHC. They all have, honestly, their pros and cons, and all have been

used in different settings to detect oncogenic fusions.

Just starting at the bottom, we all have worked with IHC forever. It is proven, and it is inexpensive. In fact, in the ALK space, it is now an approved companion diagnostic test. If there is a protein like TRK or ALK that is not widely expressed systemically in the normal adult, simple positive staining may either identify a true fusion, to be confirmed by a better method, or it may actually enrich who you may trigger reflex to in a more expensive method.

Break-apart FISH assays are like the old school visual way to see a fusion. However, remember, here we are dealing with three different genes, NTRK1, 2, and 3. They all participate in fusions. You would need a six-color FISH assay to really launch this, and it is only a single plex question. So does it make sense to develop a test for, let's call it, a 1 or 2 percent event across human cancer if you're exhausting a lot of tumor tissue to answer that one question?

PCR is problematic because TRK fusions have just so many partners, as I mentioned. If it had one partner, like ETV6, maybe you could develop a dual probe that cut across each other and develop a PCR assay.

Next-gen sequencing I think is where most people are focused, because it is comprehensive, it is hypothesis free, you can order the same panel for everybody no matter what your clinical suspicions are. But gene fusions require a lot of deliberate probe design in the setting of NGS. Specifically, remember that fusions are intronic events, and most next-gen panels are built to exon specs. The mutations would be a lot easier.

Secondly, in the case of TRK, the introns are very big. Thirdly, the fusion partners are many, as we talked about, and they are also GC rich, which is a technical issue that lab guys tell me is really important to building cost-effective probes.

There is one work-around in the NGS, which is the use of RNA instead of DNA as your testing

substrate. Unfortunately, most NGS panels deployed commercially or in academic settings are DNA-focused still.

If we could write the script for the world, we would love to see reimbursed, sensitive NGS panels widely adopted in pediatrics and adults that incorporated RNA as a testing substrate.

The next slide is just a graphic of what I told you about, the issue around fusion detections and identifying them.

MS. MCMILLAN: Then my follow-up question is if you don't get what you want, that great test sounds lovely, it would have to be a widespread. How likely can you continue to develop this agent successfully without that comprehensive, wide-scale testing?

DR. BILENKER: We have worked with a handful of centers that are themselves at least dedicated to comprehensive testing, and many of these centers have had to be creative in the way they have sourced funding and technology to, in fact, do that.

We have that slide in our main deck, where we showed the child with the different TRK fusion cancers, and there truly are some development footholds there, at the very least. Infantile fibrosarcoma, again, is a 90 percent TRK event. That is a very, as you know, rare clinical problem.

ETV6 is a frequent, but certainly not the only partner. We are benefiting a little bit from happenstance ETV6 detection.

Slide up.

I guess we would say to you guys and the academic world, it is not just about us. There is a whole list of molecular targets that are worth looking for in virtually all of the pediatric diseases where there is unmet need for systemic therapies.

I guess we are trying to do our job as a therapeutics company to interact with the best and brightest in the diagnostics world and say you guys need actionable content that is read off of your panels and your kitted assays. And here are some of our thoughts about why it matters for TRK, and

exciting stories like 101 and others, we think, will be your future with regard to reimbursement and adoption, which are the things you care about.

We try to tell this narrative whenever we can and when we are interacting with sites. But in the short term, the way we are handling it for enrollment, again, is we work with the committed, which makes our site numbers much fewer than most oncology clinical trials.

Number two, we get lucky now and then that patients are identified through ETV6 probes or they happen to be reflexed to a place like Foundation Medicine or another good reference lab.

Right now, we are getting lucky, but it is our hope that -- we know it is very -- when you see the drama of these clinical results in children and adults, it haunts you to think that there are patients out there in cancer clinics with sarcoma, say, or with thyroid cancer who have exhausted radioactive iodine, who just haven't been detected yet.

We feel like all we can do is tell our story

and encourage others to look harder.

DR. PAPPO: Thank you.

Dr. Armstrong?

DR. ARMSTRONG: My question actually had been pretty similar about the testing. Just in light of that, your third arm on the SCOUT trial, it's the non-fusion TRK genetic alteration cancers. What actually is going to be on that arm?

DR. BILENKER: Just to be super clear, those SCOUT trial concepts are in development. They are not formal protocol amendments yet, but you focused on -- slide up.

Just to remind everybody, the third box I think is what you are referring to.

DR. ARMSTRONG: Yes.

DR. BILENKER: That can encompass a few categories, amplifications, mutations, and even other diseases where TRK signaling -- like diseases of the neural crest where maybe TRK signaling is important. There are settings like DIPG where we often don't have a biopsy diagnosis, but there is some clinical suspicion that it may be there as a

fusion.

If you like, I can tell you a little bit about our thinking around TRK mutations and amplifications and what we know and what we don't know. Would that be interesting?

DR. ARMSTRONG: I think that is going to be a good target, like fusion.

DR. BILENKER: We actually don't for mutations. We don't know for amplifications, but I can explain why, if it's interesting.

Slide up.

Here is what a beautiful mutational activating mutation story looks like. I will point you first, this is the V600 BRAF story, and I will point you to the Y-axis first, where it goes up to 625 on the Y-axis. We pulled this off of the cBioPortal resource at Memorial Sloan Kettering.

You will see that the classical V600E mutation in BRAF is heads and shoulders above the other described mutational events that have now populated the databases and literature.

Next slide.

Here is what, for example, the NTRK2 story looks like. Focus first on the Y-axis, where it only goes up to 5, and you can see it is really a panoply of mutations. You don't see that classical hotspot histogram, which is a bit of a molecular epi tell that it is activating.

Next slide.

There is also a handful of other questions you can ask. Is it nonsynonymous? Is it expressed? Does it occur in the kinase domain? Does it occur in the absence of other known oncogenic drivers?

We actually did an analysis of these questions and parsed the literature -- next slide -- and showed a poster at ASCO last year, where basically we looked at over 1800 distinct mutations reported across NTRK1, 2, and 3. There were no hotspot signals, as I mentioned earlier, and most reported TRK mutations, unfortunately, have no detectable expression. Only a small minority, at least by our read, were worth looking at.

But we do have patients who self-refer or their doctors refer because they have a mutation call on a path report, and we have now a framework to think about its likelihood of activating. There is a single digit percent of TRK mutations that we think are probably worth the clinical question.

Just a brief word about the amplification story, which was a little earlier.

Next slide.

Here is a scatter plot showing a story that we think is very compelling for amplification, namely, HER2, and a story for TRK, which is, I'd say, less compelling. What you see in the scatter plot for HER2 is you see a significant number of copies, and you see that they are expressed. For TRK, we don't see that same copy number increase generally across published literature and that doesn't correlate with expression.

Again, this is directional for any given patient. An amplification story may be activating, may be interesting. We have enrolled some in our adult phase 1, and we're following them. We expect

to probably enroll some in pediatrics.

DR. PAPPO: Thank you.

Dr. Glade Bender?

DR. GLADE BENDER: First of all, I would like to congratulate you for what has been an exquisitely clear presentation. I really appreciate that.

DR. BILENKER: Thank you.

DR. GLADE BENDER: My first question has to do with, then, given the platform for the NCI-MATCH, how likely do you believe that it will be to pick up these TRK mutations and refer patients to that trial?

DR. BILENKER: In short, it's good, but not great. The Thermo Fisher Oncomine panel was okay. The focused panel is much better. The content continually improves, and so as additional fusion partners are identified and can be incorporated in the assay, that is all the better.

In the clinical development, you don't have to catch everybody to make this work. You have to catch enough, and ultimately, it is our hope that

we, with NCI-MATCH or with our own trials, kickstart this feedback loop of excitement where people decide that TRK fusion cancers matter and are worth looking for and are actionable and that leads to more and better testing.

That is really our hope, but it is good enough to be worth the effort is the concise answer.

DR. GLADE BENDER: Then a different question. You made the comment before that we all believe that more is better. I am not sure I believe that for these kinds of targeted agents. I think there is probably an optimal biologic dose. It looks like you are even there, and because what we are talking about are young kids and you have alluded to effects potentially on neuro development, maybe more is actually worse.

I wonder if, again, preclinically, you have any long-term toxicity data in juvenile animals and, also, if there is any cumulative toxicity, as we have seen with other kinase inhibitors.

DR. BILENKER: I am glad I don't have to

make the clinical decisions that you all make. Just to paint for you a case study that we encounter, and this is a typical case study, is you have a patient. They are doing well on the drug, the dose. They are responding dramatically. You get the PK back, and it is in the lower quartile of the population exposures you have seen, even at that dose.

You have the protocol flexibility to increase. The patient is doing well. There are no adverse effects. The question is what do you do. Do you stand pat, stay at that dose for that patient when you know comparable exposures have been well tolerated in other patients, or do you go up? Will you be able to catch up later in the setting of clinical progression if that were to occur?

Those are the kinds of questions that get wrestled with, and we wind up deferring to our clinical team.

I don't know, Dr. Laetsch, do you want to add to this debate, or should I leave you alone?

Then when he is finished, I can tell you a little bit about our preclinical package.

DR. LAETSCH: I am Theodore Laetsch. I am a pediatric oncologist at UT Southwestern and an investigator on the Loxo-101 phase 1 study and a consultant for Loxo.

I think that is an excellent question, Dr. Bender, and it is a struggle. I think there are competing interests. It certainly seems like there is an optimal biologic dose for which we are close for peripheral tumors. I think there is certainly a concern that for CNS tumors, we don't know yet whether or not we are at the appropriate dose for those.

I think in this study what we have done is in consultation with Loxo, but the group of investigators for the patients who review the toxicity of the patient, review the pharmacokinetic data and review the toxicity that we have seen in other patients and try to make a decision about whether or not to dose escalate individual patients and also whether or not to increase the starting

dose or increase the dose level for patients on this study.

DR. BILENKER: Slide up.

A quick answer to the question on preclinical, here is a snapshot of our current tox package that supported the IND, and it is fairly standard. We have rat and monkey as the chosen species, and we have the usual 28-day dose ranging stuff, 42. We have a range of safety pharmacology studies looking at specific questions, like hERG issues, motility, neurobehavioral even. I mentioned those rotarod experiments that we conducted. We tried to explore the full range of CNS effects.

Just to put that in some developmental framework -- next slide -- the 28-day study, as I just listed, if you look at the age of the animals, the rats, those are actually equivalent to age 12, so not perfect. I guess it does qualify as, quote, "juvenile," but not younger.

Can you switch these slides?

We noted a literature, where some folks in

this room may have had a role, where the FDA recently tackled this question. They concluded -- I just defer to the grace and wisdom of FDA on this topic, but the ICH S9 suggested that juvenile animal experiments did not meaningfully contribute to an understanding of risk in human patients. They didn't provide useful information. They didn't affect first pediatric dose and that really it was longitudinal follow-up which was going to be the ultimate test of the pediatric safety question that we all care about.

Can I have the other slide back?

However, we recently engaged with European regulators, and they felt slightly differently on this topic. So we are going to conduct some studies in younger animals. We have an additional toxicology study planned that will begin at 7 days old in the rat and being dosed through 56 days of age, which is equivalent to human years of neonate through young adult.

We are going to look specifically at issues that affect pediatric health, like bone length,

reproductive endpoints, behavioral issues, and, of course, have histopathology in there, too.

DR. PAPPO: Thank you.

Dr. Reaman?

DR. REAMAN: I am glad Dr. Glade Bender asked the juvenile animal, because that was the question I was actually going to ask. Although we feel that routine juvenile animal toxicity studies are probably not necessary, I think in this particular case, given the potential for developmental biology and neurobiology, we would have probably suggested that it be done here, also. So I am glad to hear that you are actually doing it.

I wanted to just ask about, there have been TRK fusions seen, although they may not be along with other known oncogenic drivers in hematologic malignancies, but do you have any plans to explore this product, the activity of this product in heme malignancies, as well?

DR. BILENKER: We want to go where the biology leads up, in general.

Slide up.

We are aware of this study, which you probably are, as well, where patients with BCA-negative AML, there was a gene expression study, and 44 different rearrangements were observed. There was a single patient with an ETV6 and TRK3 fusion cancer.

Some of our co-investigators are interested in this topic, especially in the setting of pediatrics. I believe there is also an adult case report of an AML patient in the literature, but I haven't seen it reproduced or confirmed.

The way we are handling the question is to I guess come to you when we've identified a patient rather than to create a standalone trial. We are exploring other ways to answer the pediatric or, I should say, liquid tumor question for this target.

DR. PAPPO: Thank you.

Dr. Warren?

DR. WARREN: I would like to circle back to the CNS issue, because I am not sure if the pharmacokinetic and toxicity profile is an obstacle

or advantageous or actually maybe even exciting for a disease entity like DIPG.

My first question is, are the toxicities, particularly neurotoxicities, reversible and quickly reversible?

The second question is, have any of your preclinical studies looked at administration of the agent directly into the CNS?

DR. BILENKER: The toxicities do seem reversible. When patients have had dizziness or ataxia or things like that, they do seem to reverse.

Slide up.

This is the safety data we presented at AACR in April from our phase 1 adult study, where we focus on 100 milligrams BID, and we have also all patients. You will see that we have some dizziness on there. We have a delirium down near the bottom. In all those cases, there did seem to be a temporal relationship, and it did reverse.

But again, most patients did not report this, and this is true of our phase 2 and phase 1

studies and peds included. We are not seeing this as a dose-limiting issue whatsoever. It almost seems idiosyncratic in the way it comes out, and there is often intercurrent variables which suggest that it may not even be the drug. But we are capturing that.

No, we haven't looked at the direct administration of the drug into the brain.

DR. PAPPO. Thank you.

DR. MacDONALD: Tobey MacDonald. You mentioned TRK fusions were observed in 40 percent of high-grade glioma in less than 3-year-olds. Have they been, to your knowledge, detected in older patients as well?

DR. BILENKER: I believe there is literature saying yes, there is, but we -- slide up.

Here is what we know about the literature, and I am sure you guys know this better than we do. I guess this is really focused on pediatric patients, and your question was, I guess, focused on adults.

But we have not seen, in our experience,

patients reported with this entity. But it has been described in the literature.

DR. MacDONALD: In that regard, in those less than 3 years of age in which there is no universally accepted treatment, since radiation is not typically an option, is there consideration for upfront infants with TRK fusions?

DR. BILENKER: Meaning if --

DR. MacDONALD: To enroll in the trial. So if you recognize a TRK fusion patient at diagnosis rather than do courses of chemotherapy, which in most cases have failed.

DR. BILENKER: The issue we struggle most with in that disease setting is the lack of a tissue-confirmed biopsy of a TRK fusion. They are hard to get, and some investigators are persistent. Some might pull it off, but we often find ourselves in an empiric setting where we have a non-tissue confirmed patient, where I think the risk-benefit analysis may preclude what you are suggesting.

But when we know there is a TRK fusion present, given the consistent efficacy we have seen

thus far, we will really do anything we can with the investigator and the agency to figure out how to get drug access for the patient, if that is what everybody feels is best.

We are completely supportive of the clinical judgment that wants to do that, but it has been the tissue confirmation that has been tricky in DIPG.

DR. MacDONALD: Just a last practical question. Is the liquid formulation compatible with NG2 gastric tubes?

DR. BILENKER: Yes.

DR. PAPPO: Thank you.

One final question. In the pediatric patients that have responded to your drug, has there been any correlation between the PK parameters and the expected dose for the adults that are 100 BID, or are they all over the place? Are you seeing responses at lower levels, and is it really necessary to keep increasing the dose, following up on your question?

DR. BILENKER: I will cheat a little bit and answer you. I am not supposed to.

But yes, we have. We have seen responses at lower exposures than we expected.

Questions to the Subcommittee and Discussion

DR. PAPPO: Thank you. I think we are done with the questions. Thank you very much.

There are no OPH speakers. We will now proceed with the questions to the committee and panel discussions.

I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Let's start with question number 1.

DR. OSGOOD: Please consider the ongoing pediatric study and provide an opinion regarding the overall study design.

DR. PAPPO: If there are no questions or comments concerning the words or the question, we will now open the question for discussion.

Dr. Weigel?

DR. WEIGEL: Brenda Weigel. I think the design is really trying to take into account this

targeting of the optimal dose, which I think is an attempt, and I applaud the attempt, to balance toxicity versus optimizing responsiveness.

I think I would encourage some real thought to how that dose is being defined and what parameters are being put around that based on the adult data, as well as toxicity data. It may be that we don't define a traditional maximally tolerated dose, but I am not sure I understand completely yet how we are defining the optimal biologic dose or the targeted dose range by pharmacokinetics. So I would encourage real thought behind the decision-making for dose selection.

DR. PAPPO: Thank you.

Dr. Glade Bender?

DR. GLADE BENDER: I am not sure I have the answer to this either, but it seems that this is such a rare disease entity that maybe we should be learning more about dose and PK by patient than cohort, meaning that I think one could start at a dose that we think might work and do the

intrapatient dose escalation, if there is any concern about the first round of PK or any concern that the response is not adequate, and learn about the different PK by dosing by patient rather than trying to fill sequential cohorts. Because I just think that it will take a very long time to get to the right dose per patient.

I also think that I'm not sure that more is better for those who would have responded to a lower dose. I think when we are dealing with a targeted agent that seems to be very efficacious for patients who harbor these translocations, maybe the trial design is an intrapatient escalation design and not a cohort design.

DR. PAPPO: Thank you.

Dr. Reaman?

DR. REAMAN: Can I just ask if the real-time PK -- how complicated is that and how realistic is it to think that it is something that could be done in every center environment? Is it something that would have to be done centrally? Could it be done at selected sites? Any special handling of the

blood once it is drawn for PK?

DR. BILENKER: The phase 1 pediatric trial is practically functioning like an intrapatient dose escalation design. We have a reliable PK method. We are performing it centrally. We tend to get results back within days and analyzed within days.

I think we are seeing what we struggle with is what are the labeling implications of this kind of approach, and ultimately it would be nicer to be able to define either a fixed dose or a weight-based dose eventually that corresponds to the exposures associated with efficacy.

We still hope that that is possible. We would be more than happy to explore an alternate route of development if that seems best for patients and the agency.

DR. PAPPO: Thank you.

Dr. Neville?

DR. NEVILLE: I had a follow-up to that, and forgive me if I missed it. Are you following AUC above the IC50, or what are we trying to correlate

with response? It didn't sound like the PK was that tight. So what are you proposing that the real-time PK is going to achieve?

DR. BILENKER: The PK is fairly tight for an oral kinase inhibitor. It is actually fairly typical, which makes it not tight, which is 5X variability across populations of patients. In pediatrics, you throw in the differences in CYP3A access and weight. We haven't noticed that it is much different, however, in peds versus adults.

What we really do is descriptive. Our PK modeling is descriptive, and we plot both. We plot Cmax, we plot AUC, and we plot just time over curve. Then we overlay our most conservative model of tumor response preclinically, which are those IC90, IC50 lines I have showed in a couple of slides.

But we have seen, quite honestly, such a range of doses delivering very robust activity that it is hard to make a specific recommendation other than to say your patient is coming in, quote, "low" relative to other levels we have seen as safe and

effective, but your patient is doing well. So there is this clinical impact conundrum of what does it mean.

That is an analysis that we think a doctor is best able to make, not the company, but yes, we just provide the information.

DR. NEVILLE: Then I would question the utility of your real-time PK. Is it really giving what you need versus just doing classic PK over time and modeling and looking at response, because it does not sound like your PK is correlating with response or toxicity necessarily?

DR. BILENKER: We are only six months into this pediatric trial. When we started, we certainly did not know how we would do, and we thought real-time PK was the safest way to at least ensure safety so we didn't overshoot or preserve efficacy in case we dramatically undershot. So we felt like this was a protocol element that would protect us a bit, and the investigators seemed to embrace it.

I think you are right, though. As we gather

more information and the PK/PD relationship or PK-efficacy relationship may be wider or more elastic than is typical for most drugs, it might give us the high-class problem of choosing among lower doses.

But to us, it is a speculative exercise. The thing we care most about really is durable efficacy, and the durable efficacy part is only known over time. It is a drug development conundrum. What do you do? You won't know for even months or years what you may have left on the table, and given the rarity of these patients, it is hard to really be perfect about it.

We are just trying to, therefore, give what doses we know are safe and then to let clinicians weigh in on what balance of safety versus durable efficacy trade they want to make.

DR. GLADE BENDER: I just want to go back, because I think I left one of my questions on the table.

Do you have any evidence of chronic toxicity, because I have noticed that one of the

patients on the study was started at 150 BID and actually went down to 100 BID? And at least with the other kinases that we have studied, that seems to be a problem that they can tolerate the higher dose for a short period of time, but then they have to go down anyway.

DR. BILENKER: We have seen no evidence of chronic toxicity rising up later, and the phase 2 will be the best measure of that where we are hopefully following patients for a long period of time, whereas the long clock runs, we will get a better sense of that.

I think that particular patient had some kind of intercurrent AE that was probably unrelated to the study drug. We dose de-escalated, restarted, and there were no issues. But I wouldn't overread any one of these patients. It is a fairly complicated fact pattern in most cases.

But again, we are not seeing any trend whatsoever in our adult phase 2. We have had patients on since October, and then all of our responders in the phase 1 setting they are on, so

we have patients now, as you saw, well into the one-year mark.

DR. PAPPO: Just a comment to try to please limit your comments to the question.

I am going to try to summarize this, and it is going to be complicated. So I am going to need a little bit of help.

(Laughter.)

DR. PAPPO: First of all, I think that the committee was extremely impressed. It was a very, very lucid presentation. We are also extremely excited that you are bringing this agent for our very rare subgroup of pediatric tumors and that there is a lot of interest in conducting phase 1 studies in pediatrics early on.

One of the questions that the committee is struggling with is how to best define the optimal dose for this group of patients and how to identify the optimal biological dose for these patients. Although we do not have an answer, one possibility would be to do basically intrapatient dose escalations but get your dose and PK based on

individual patients, not on cohorts of patients.

Also, it is unclear what the utility of real-time PK is in these patients, given the fact that responses have been observed and that is unclear whether increasing the dose of certain number of patients will increase the efficacy and potentially could increase toxicity.

I think most of the questions on chronic toxicity and neurological toxicity have been answered very, very clearly.

Did I leave anything out?

DR. WEIGEL: (Inaudible - off mic.)

DR. PAPPO: Thank you.

We will now move to question number 2.

DR. OSGOOD: 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.

DR. PAPPO: If there are no questions or

comments concerning the wording or the question, we will now open the question for discussion.

Dr. Reaman?

DR. REAMAN: I want to say it is encouraging to hear that the safety profile actually sounds pretty good, given the target that is being inhibited by this product. My only concern would be in very young children, and I think there are plans to slowly enter that space. I think it is a space that has to be entered, because my experience with infantile fibrosarcoma has always been in babies under 6 months of age.

I think there is a very unique opportunity there, provided the juvenile animal tox studies permit, to really look at the issue of PK and intrapatient dose escalation and toxicity.

DR. PAPPO: Thank you.

Any other comments or questions?

Yes, Dr. Weigel?

DR. WEIGEL: I applaud the effort to systematically collect very detailed neurotoxicity data and would encourage you to really be detailed

and focused on that, and that is going to be a very important part of the contribution for deciding on dose.

DR. PAPPO: Julia?

DR. GLADE BENDER: I was going to say what Brenda said.

(Laughter.)

DR. PAPPO: Yes, Dr. Armstrong?

DR. ARMSTRONG: Just the observation that you treated a 16-month-old with the adult dose would suggest that you probably got higher levels in that infant than you are getting in the adult and that it is still biologically active in the adult at 100 milligrams BID. That issue of MTD versus biological dose I think is actually one that we would hope you would continue to explore in both the adult and pediatric populations.

DR. PAPPO: Any additional comments or questions?

Yes, Dr. Neville?

DR. NEVILLE: I can just say, to reiterate what has been discussed previously, we should be so

lucky as to have to live with the long-term toxicities. I think as you dose optimize, we will have to figure out what they are, but we accept a lot of toxicity for saving lives. So I don't know that we can discuss mitigation of that yet.

DR. PAPPO: Thank you.

The committee feels that the safety profile of the drug appears to be very favorable. This protocol offers a unique opportunity to study not only the activity but the pharmacokinetics and the short- and long-term toxicities of this drug in a unique group of patients, which are young children afflicted with tumors such as infantile fibrosarcoma or hemangiopericytoma.

We also encourage you to keep looking at the long-term effects of this drug, specifically neurotoxicity, and the issue of how to better define the dose of this drug for this group of patients, whether it is MTD uptake or biological dose or other, needs to continue to be explored.

Does that pretty much sum it up?

Okay. We'll go to question number 3.

DR. OSGOOD: Please consider the necessity for an international collaborative study, given the very rare cancers for which Loxo-101 may prove relevant.

DR. PAPPO: If there are no questions or comments concerning the wording or the question, we will now open the question to discussions.

Yes, Dr. Brown?

DR. BROWN: Can I ask how prevalent is this testing that's required to detect this lesion in an international setting? It is a question, not a statement, and I don't know if anybody has the answer. But that is what I'm wondering.

DR. REAMAN: It is probably more prevalent in Europe than it is here, I would think.

DR. BROWN: Just to follow up then, I think it would be very relevant to include the national sites.

(Laughter.)

DR. PAPPO: Probably with a phase 2, I think.

Julia?

DR. GLADE BENDER: I was going to say, we should state the obvious. Of course, with a rare entity, we should encourage international collaboration. And I think with other countries that have nationalized health systems, your likelihood of getting generalized testing is probably higher.

DR. PAPPO: Thank you.

Yes, Dr. MacDonald?

DR. MacDONALD: Just to follow up on that, outside of a formal consortium, I would seek early discussions from pediatric leadership as to what sites have the volume and the ability to do this type of testing that you seek. I don't think it is intuitive necessarily, and it may not be based on the adult centers in terms of their pediatric volumes and ability to do testing. So I would get early insight into that.

DR. PAPPO: Dr. Reaman?

DR. REAMAN: I think that is a good point, but I think there is also a role for centralized testing. It is possible that the patients are

going to come from multiple centers, but having a centralized resource that can do the kind of testing that is required is certainly another option and perhaps a better option, given the rarity of these tumors?

DR. PAPPO: Yes?

MS. MCMILLAN: Gigi McMillan, patient representative. Along those lines, I think that it could be a novel consideration or even unexpected for a parent to think that once their child is diagnosed with cancer, they have to have complete genomic profiling.

While I understand that this agent would benefit from that kind of routine testing, I think that somewhere in our comments we have to address the fact that it can be surprising for a parent to realize that at the last moment or at this moment of diagnosis that, okay, we are going to have a complete test done, because there are all the usual genetic questions: who is going to hold the data; how is it safeguarded?

That kind of a decision is separate or that

kind of consideration, reflection is separate than what is the best thing for my child. I feel like we need to put that in our comments.

DR. PAPPO: Thank you.

Any additional comments?

(No response.)

DR. PAPPO: The committee supports international collaboration, especially if you are going to move this into subgroups of patients with very rare tumors. We also encourage you to explore the availability of genomic testing in specialized sites, especially in Europe, or consider the possibility of centralized testing.

Anything else?

(No response.)

DR. PAPPO: We will now move to question number 4.

DR. OSGOOD: Please comment on the adequacy of the current pediatric formulation and any plans for evaluation of the pediatric formulation.

DR. PAPPO: If there are no questions or comments concerning the wording or the question, we

will now open the question for discussion.

Brenda?

DR. WEIGEL: I think the formulation seems very appropriate, and there is a liquid formulation, allowing dosing in very small children, which is a significant advantage.

DR. PAPPO: Thank you.

Any other comments?

(No response.)

DR. PAPPO: The committee feels that you have the appropriate formulation. It is an advantage to be able to give it to young patients.

Thank you.

The final question, question number 5.

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

DR. PAPPO: If there are no questions or comments concerning the wording or the question, we will now open the question for discussion.

I think this is an issue that we have been

discussing throughout the whole thing and the pros and the cons of different platforms, whether it is FoundationOne or whether it is IHC or whether it is a specific PCR. There are very, very few centers that have routinely more comprehensive testing, such as whole genome sequencing or exome sequencing.

The issue with whole genome sequencing is that you need fresh tumor. The issue with exome sequencing is that sometimes it is not paired with RNA-seq. Sometimes you only do the tumor. You don't do the germline.

I think there is a lot of variability with this, and I really do not know what the common practice is. Most of the time when you get a patient with infantile fibrosarcoma, by default, you look for the fusion by PCR or you just do FISH, but as you said before, there are so many variables that you might be missing, novel partners.

I don't know what the best way is to address this issue.

Dr. Reaman?

DR. REAMAN: I would think that maybe some of it should be diagnosis dependent. I think looking for NTRK-expressing tumors is one thing, but then having specific diagnoses where we know that the incidence is increased, I think then doing whatever specialized test looking for it would certainly be something that would be clinically almost standard of care.

But I do agree with Ms. McMillan's point. But I think we are really entering a whole new phase of cancer therapy, looking at specific gene expression and molecular phenotype of tumors to predict potential therapies both at diagnosis in certain situation and certainly in early phase settings, looking for appropriate targeted therapies. But it does come with considerations and questions that patients and families really do have to consider and address.

DR. PAPPO: Thank you.

Julia?

DR. GLADE BENDER: I actually want to second what Dr. Reaman said about diagnosis-driven

comprehensive testing, because as I was thinking about it, I think that two of the large series that have been recently published, both out of Michigan and that of the iCAT Dana Farber Consortium multicenter study, both of those studies, it was this diagnosis of infantile fibrosarcoma where they found novel NTRK fusion patients.

I think that the diagnosis-driven idea is an excellent one.

DR. PAPPO: Yes, Dr. Warren?

DR. WARREN: I think we need to consider making it mandatory that these be done in a CLIA-certified lab and having them validated in a second laboratory.

DR. PAPPO: Any additional comments or questions?

(No response.)

DR. PAPPO: Regarding this question, we believe that certainly certain histologies in which you expect to have an NTRK fusion, this should be pursued thoroughly. It might be diagnostic specific, and this has to be done in a

CLIA-certified lab.

The issue of genomic testing either at the time of diagnosis or relapse, it really depends a lot on independent institutions, but we strongly encourage that at least if you have any of the diagnoses that you have shown that have a high probability of having an NTRK fusion, that this should be pursued very thoroughly.

Anything else?

(No response.)

DR. PAPPO: We are going to take a break now. Let me read so it sounds very official. We will now take a between 15- and 20-minute break.

Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience.

We will resume at 10:00 in the morning. Thank you very much.

(Whereupon, at 9:43 a.m., a recess was taken.)

DR. PAPPO: We are going to get started.

Steve, can you state your name for the record?

DR. DUBOIS: Steve DuBois. Dana Farber Boston Children's.

DR. PAPPO: Thank you.

We will now proceed with topic 2, entrectinib from Ignyta, Inc. Dr. Lauren Tesh will read the conflict of interest statement for this session.

Conflict of Interest Statement

DR. TESH: The Food and Drug Administration is convening today's meeting of the Pediatric Subcommittee of the Oncology Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of

this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws under 18 U.S.C. Section 208. Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to effect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential

financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

This session's agenda involves information to gauge investigator interest in exploring potential pediatric development plans for five 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 product under consideration for this

session is entrectinib, presentation by Ignyta, Inc. This is a particular matters meeting during which specific matters related to Ignyta's product will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Drs. Pappo and DuBois.

Dr. Pappo's waiver involves his employer's current study with the potentially affected firm and product anticipated to be between 50,000 and 100,000 per year in funding.

Dr. DuBois' waiver involves his employer's current study of entrectinib funded by Ignyta which is estimated to be between 0 and $50,000 per year in funding. Dr. DuBois' waiver also involves his employer's current study with a potentially affected firm estimated to be 0 to 50,000 per year in funding. Lastly, Dr. DuBois' waiver involves his consulting agreement with a potentially

affected firm, which he receives between 0 and $15,000 per year.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted at the FDA's website. Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fisher's Lane, Room 1035, Rockville, Maryland 20857, or a request may be sent via fax at 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. P.K. Morrow is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Morrow's role at this meeting is to represent industry in general

and not any particular company. Dr. Morris is employed by Amgen.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they might have with the firm at issue.

Thank you.

DR. PAPPO: Thank you.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the sponsor's presentation.

Industry Presentation - Pratik Multani

DR. MULTANI: Thank you.

Good morning, Pediatric Advisory Committee members, FDA representatives, ladies and gentlemen. I am Pratik Multani, and I serve as Ignyta's chief

medical officer. It is my pleasure to represent my colleagues here today to summarize our clinical development program of entrectinib, as well as our pediatric development plans.

During this presentation, I will provide an introduction to entrectinib, including a summary of our extensive preclinical data in phase 1 adult clinical experience. I will then review our rationale for pediatric development, followed by the design of our ongoing phase 1/1b pediatric clinical trial.

Entrectinib is a small molecule tyrosine kinase inhibitor with cellular activity against the five receptor targets listed here, TRKA/B/C, ROS1, and ALK. It has biochemical potencies against these targets that are in the single digit nanomolar or picomolar range.

These proteins are encoded by the five genes, NTRK1/2/3, ROS1, and ALK, respectively, which can become oncogenic drivers when rearranged or otherwise activated in a constitutive fashion.

Entrectinib also demonstrates inhibitory

activity against most of the known TRK-resistant mutants. Entrectinib was specifically designed to cross the blood-brain barrier, giving it the potential to treat primary and metastatic brain tumors, which is a common complication of many cancers, including pediatric cancers.

We have tested entrectinib in a large series of preclinical xenograft and patient-derived xenograft models. Depicted here are four representative models demonstrating the ability of entrectinib to achieve profound tumor growth inhibition, including regression in models of NTRK1, NTRK3, ROS1, and ALK gene rearrangements.

Pediatric development and providing early access has been an integral part of our plan from the outset of this program. In particular, in neuroblastoma where overexpression rather than gene rearrangements may be an onco driver, we evaluated the potential of entrectinib across multiple models systems.

ALK has already been recognized as a potential therapeutic target in neuroblastoma, and

here are in vitro data in a model of neuroblastoma characterized by ALK overexpression, showing inhibition of cellular proliferation with entrectinib treatment.

Through our collaboration with Children's Hospital of Philadelphia, we expanded the potential target list to neuroblastoma by exploring TRKB overexpression as an independent onco driver. Autocrine activation of the TRKB BDNF pathway has been reported in 50 to 60 percent of high-risk neuroblastoma cases, and TRKB overexpression appears to occur in the majority of patients and is associated with invasion, metastasis, and chemo resistance.

Here, you see the ability of entrectinib to inhibit tumor growth versus control and extend event-free survival in a model of neuroblastoma employing a cell line driven by overexpression of TRKB. Of note, the specific model system was selected because it is not responsive to ALK inhibition. Similar results were obtained in three other TRKB expression driven neuroblastoma models.

We acknowledge that entrectinib in combination with standard chemotherapy agents, it is important to explore in addition to single agent treatment. For example, we have observed additive activity of entrectinib when paired with irinotecan and temozolomide in the same TRK-driven preclinical model of neuroblastoma.

Together this preclinical package forms the basis of our interest in taking entrectinib into neuroblastoma, among other TRK-driven malignancies in children.

Here, we have the preclinical data that support the potential of entrectinib to penetrate into the CNS and treat primary and metastatic CNS disease. Entrectinib demonstrated penetration into the brain in all three nonclinical species tested. It was highest in dogs, where brain levels exceeded blood levels.

On the bottom in this preclinical model of metastatic disease using outdriven, non-small cell lung cancer cells, a 10-day treatment with entrectinib limited tumor growth and extended

survival.

In terms of its nonclinical profile, entrectinib is highly plasma protein bound. It is cleared primarily through the liver. In nonclinical toxicology studies, CNS-related effects were seen in both species studied.

Rats exhibited incoordination and decreased activity, while dogs, the species with the highest brain exposure, exhibited incoordination, tremors and hypoactivity. These effects, however, were all reversible, and no histopathological findings were seen in the brain of either species or in the dorsal root ganglia of dogs.

Overall, based upon toxicology studies, all adverse effects observed in humans were identified in nonclinical species, and standard clinical monitoring using clinical findings, ECG, and lab values has, therefore, be deemed adequate monitoring for adults in our ongoing studies.

Let's now turn to the clinical and regulatory program. The first-in-human-trial ALKA-372-001 was initiated in Italy. Subsequently,

the STARTRK-1 trial, another Phase 1 study, was initiated in the United States.

Since then, multiple orphan designations have been granted, the first being our orphan designation and rare pediatric designation in neuroblastoma in late 2014. The EMA also granted orphan designation for neuroblastoma in late 2015.

As I stated previously, pediatric development and providing early access has been a priority for us. So shortly after we identified the recommended phase 2 dose, the adult global phase 2 study, STARTRK-2, began in September of last year, which was quickly followed by the initiation of our pediatric phase 1/1b STARTRK Next-Generation trial.

(Laughter.)

DR. MULTANI: Now, to summarize our adult clinical experience. Ignyta has conducted two concurrent phase 1 studies in adults with advanced solid tumors, which collectively explored regimen and dose in order to arrive at an empirically-derived optimal human dose and dosing

schedule.

In view of the neuronal biology of TRK receptors, the first in human ALKA study initially studied an intermittent dosing schedule. After completing full dose escalation without dose-limiting toxicity, the ALKA study then proceeded to evaluate a continuous dosing regimen, which is now the preferred dosing schedule due to consistent target coverage and acceptable safety, as I will show in a few minutes.

From this study, as of a data cutoff of March 7th, 2016, we have enrolled 54 patients from two centers in Italy. The second study, STARTRK-1, began with continuous dosing and as of the same date of cutoff, we enrolled 65 patients. Combined, this represents a total clinical experience of 119 adult patients in the phase 1 setting alone.

Through this experience, we identified 400 milligrams per meter squared as the BSA-based recommended phase 2 dose in adults followed by 600 milligrams fixed dose, which has now been established as the recommended phase 2 dose of

entrectinib in adults on a once-a-day continuous dosing schedule.

The majority of patients enrolled in these two studies did not have the gene rearrangements of the targets of entrectinib. So most of the patients would not be considered candidates for response to entrectinib treatment. We did, however, enroll 25 patients who had gene rearrangements of NTRK, ROS1, or ALK who were naive to prior treatment with a TRK, ROS1, or ALK inhibitor and were treated at or above the recommended phase 2 dose.

The efficacy evaluation that I will present later will focus on these 25 patients, 24 of whom had extracranial solid tumors and one with a primary brain tumor.

This slide presents the most frequent all causality adverse events across all 119 patients, as well as the most frequent treatment-related adverse events. It includes patients who received entrectinib above the recommended phase 2 dose.

As you can see, the majority of adverse

events are grade 1 or 2 in severity, with only a few grade 3 or 4 adverse events. These events, when associated with entrectinib, were reversible in all cases. Many are attributable to on-target TRK inhibition, such as dysgeusia and parathesias.

Acknowledging the brain penetrant properties of entrectinib, you will notice that the toxicities clearly attributable to the CNS are largely absent from both lists, with the exception of grade 1 or 2 dizziness in 19 percent of patients in the all causality column.

In addition, we have seen no evidence of cumulative toxicity, hepatic, or renal toxicity, or evidence of QTc prolongation to date.

Overall, we feel the safety experience supports further clinical development in adults and clinical development in children.

We now turn to efficacy. As I said earlier, most patients enrolled did not have one of the gene rearrangements that is targeted by entrectinib, but 25 out of 119 patients did have one of these gene rearrangements, were naive to prior treatment with

an inhibitor of these targets, and received a phase 2 dose or higher.

This figure shows the maximum measured tumor reduction for each of the 24 patients with extracranial solid tumors. All patients except for two had some tumor regression, and 19 of these 24 patients, or 79 percent, had confirmed responses by RECIST criteria.

Responses were seen in patients with each of the targets of interest; 3 out of 3 or 100 percent, of NTRK patients responded, 12 out of 14 or 86 percent of ROS-1 patients responded, and 4 out of 7 or 57 percent, of ALK patients responded.

Finally, one additional patient, the 25th patient, had an NTRK-positive astrocytoma. This primary brain tumor also showed evidence for tumor regression. This patient had stable disease by RECIST criteria, but since RECIST is not validated for brain tumors, the clinical center performed volumetric analysis, which showed 45 percent tumor regression. In addition, he had significant improvement in his associated clinical symptoms.

This slide represents the time on study for each of the 24 patients. We have treated patients with many different tumor types, including non-small cell lung cancer, salivary gland cancer, colorectal cancer, metastatic melanoma, and primary brain tumors. As you can see, there is strong evidence for durability of response. The longest patient in response is a patient with ROS1-positive non-small cell lung cancer, who was close to 27 months on entrectinib as of the date of cutoff.

We have multiple additional patients who have been on entrectinib for more than a year, and the entrectinib patient with the longest duration of response is at 12 months as of the date of cutoff.

You will note that the time of response is also brisk. The diamonds represent the time to response, which is 4 weeks or 8 weeks for most patients.

Here, we have an example of a patient treated on one of our phase 1 studies. This is a 46-year-old man with NTRK1-positive non-small cell

lung cancer who, before enrolling onto the STARTRK-1 trial, had received multiple prior therapies, including anti-PD-1 therapy. He was also found to have 15 to 20 brain metastases prior to coming on study. He was very sick, with poor performance status, and the patient was in hospice at the time of study enrollment.

You can see his baseline CT scans, which show extensive tumor in his lungs. After approximately 4 weeks of entrectinib therapy, he had almost 50 percent reduction in tumor, and more recent scans at almost 11 months show continued response, with additional tumor regression.

Here is a case of another patient, a 22-year-old woman with neuroblastoma, with an activating point mutation of the ALK gene. She had multiple lines of prior therapy before receiving entrectinib, and she achieved a partial response and remained on entrectinib for over 3 years.

These scans show the brain metastases of the patient with non-small cell lung cancer I described earlier. The baseline scan shows 2 of his 15 to 20

brain metastases. By 4 weeks, he had a complete response in the brain, and his complete response has continued.

The second case is of a 53-year-old Korean woman with ROS1-positive non-small cell lung cancer, and you can see the rapid response within 7 weeks of her ROS-1 positive brain metastases.

Finally, we have a case of a patient who came to us as a compassionate use request off study. The case is of a 20-month-old baby boy with a recurrent metastatic infantile fibrosarcoma. He presented at birth with this malignancy, necessitating amputation, but unfortunately, he recurred in the lungs, for which he received chemotherapy.

At age 1 year, he had another recurrence this time in his brain, which was resected, followed by chemotherapy. It was at the time of his second CNS recurrence that he was brought to our attention. He was clinically severely impaired by the extent of his CNS disease, with a statement from his treating physician that "death was likely

imminent."

At baseline prior to entrectinib, he had a large tumor mass in the right hemisphere, centering on the right temporal lobe, with massive tumor-related swelling and a 17-millimeter midline shift with evidence of transtentorial herniation.

As of the date of cutoff, after 5 weeks on entrectinib, his follow-up scans demonstrated significant decrease in the size of his tumor, with improvement in edema and resolution of mass effect. More importantly, he was back to eating and crawling.

Thus, in conclusion from our phase 1 experience, we have shown that entrectinib appears to be well tolerated based upon a treatment experience of 119 patients. The safety experience consists of many patients who have received entrectinib for extended periods.

We have seen an overall confirmed response rate of 79 percent, with responses in patients with TRK, ROS1, or ALK-positive extracranial solid tumors. These responses can occur as quickly as

4 weeks and have good durability, and importantly, we have seen responses across multiple tumor types. We have also seen complete and durable response, including patients with primary or bulky metastatic CNS disease.

Now, switching to consideration of the pediatric patient population. The NTRK gene rearrangements against which we have seen initial clinical activity with entrectinib in the adult patient population are also seen in children, leading to the hypothesis that TRK inhibition in the appropriate setting may impart clinical benefit.

Some tumors such as primary glial tumors and papillary thyroid cancers are seen across the age spectrum from adults to children. On the other hand, other tumors are largely exclusive to the pediatric population, and moreover, in some instances, for tumors such as congenital or infantile fibrosarcoma or secretory breast cancer, the tumors may be defined by the presence of one of these gene rearrangements such as ETV6, NTRK3 in

infantile fibrosarcoma.

Of note, a subset of glial tumors in children called diffuse intrinsic pontine gliomas may also be enriched in NTRK gene rearrangements.

Finally, as discussed earlier through an alternate mechanism of TRKB overexpression, neuroblastoma may also be amenable to TRK inhibitor therapy. This finding of TRKB overexpression is also seen in anaplastic Wilms tumor, medulloblastoma, and retinoblastoma, making them also potentially amenable to TRK inhibitor therapy.

ROS1 activating alterations have also been identified in some pediatric tumors, including ROS1 gene rearrangements in inflammatory myofibroblastic tumor, and overexpression in congenital fibrosarcoma.

Finally, ALK alternations are seen in inflammatory myofibroblastic tumor, as well as a range of activating point mutations in neuroblastoma.

Nevertheless, despite their broad distribution, these molecular findings, these

tumors are extremely rare, most with case rates fewer than 10 per million.

We initiated our phase 1/1b pediatric clinical trial of entrectinib at the end of 2015. The patient population under evaluation is children age 2 to 21 years with relapsed or refractory neuroblastoma, extracranial solid tumors with or without NTRK1/2/3, ROS1, or ALK gene rearrangements, and primary CNS tumors.

We selected our starting dose based upon our adult experience in order to achieve a potentially therapeutic exposure with the first dose level. Considering the strong scientific rationale for pediatric development, the compelling preliminary clinical efficacy and large safety profile in adult cancer patients, and an available formulation that was deemed suitable for children able to swallow capsules, we began the study with the current adult capsule formulation, with the intention of introducing into the study a pediatric granule formulation as soon as available.

We elected granules in consultation with our

pediatric investigator as a liquid formulation of this compound was not feasible.

We also feel that some pediatric patients may prefer oral capsules over granules mixed with food, and thus it would be prudent to test both formulations in the pediatric population in order to ensure adequate PK and safety experience.

The study itself has a stepwise design. The initial part A seeks to establish a pediatric recommended phase 2 dose in patients with extracranial advanced solid tumors using a 3-plus-3 dose escalation design.

We then moved to three simultaneously enrolling cohorts. Part B revisits dose escalation in patients with primary CNS tumors. Part C explores entrectinib at the phase 2 dose in patients with neuroblastoma using a Simon's two-stage design. Finally, part D explores the efficacy of entrectinib in pediatric patients with solid tumors that harbor gene rearrangement of NTRK1/2/3, ROS1, or ALK.

In all instances, tumor genomic profiling is

performed, but only part D requires a positive result as a condition for enrollment.

Response is assessed by RECIST, with the incorporation of the Curie scale for neuroblastoma and the use of RANO for children with brain tumors.

In selecting our starting pediatric dose, we began with our adult PK data, and the exposures we were able to achieve both at the adult RP2D of 600 milligrams fixed and at the lower dose of 200 milligrams per meter squared.

You will note that both PK profiles are multiple folds above the entrectinib IC90 based upon preclinical xenograft models, and this coverage is maintained over a full 24 hours with once-a-day dosing.

Based upon these data and along with PBPK modeling, which took into account differences in physiological parameters such as enzyme transporter expression levels, GI transit, et cetera, and the body size at various age groups both through weight and BSA, we selected 250 milligrams per meter squared to provide an initial safety margin while

still maintaining therapeutic potential.

Dose escalation begins at this dose and then quickly moves to 400 milligrams per meter squared, which, as I said previously, is our adult BSA base recommended phase 2 dose. The protocol allows further dose escalation beyond this dose level up to 750 milligrams per meter squared once daily.

In the primary brain tumor cohort, we revisit dose escalation by dropping down on dose level from the previously established RP2D in children and then dose escalating from there.

As I stated, the primary objective of this study is to identify a phase 2 dose in patients with relapsed or refractory extracranial solid tumors and then in patients with relapsed or refractory primary CNS tumors. The secondary objectives are as expected.

Additional eligibility criteria include measurable or evaluable disease with a performance status of greater than 60 percent and a BSA greater than or equal to 0.45 per meter squared.

In terms of safety monitoring, as I

summarized previously, to date, from the adult phase 1 experience, there's been no evidence of cumulative toxicity, concerning CNS toxicity, hepatic or renal toxicity, or QTc prolongation.

During the dose escalation, patients will be monitored for dose-limiting toxicities, including special attention to CNS toxicity. In general, entrectinib will be interrupted for adverse events of grade 3 or greater, with resolution of toxicities down to grade 2 or lower or at baseline before resuming treatment.

Specific to this pediatric trial for adverse events of somnolence or cognitive disturbance, toxicity must resolve to grade 1 or lower or baseline before resuming treatment.

We will be collecting extensive pharmacokinetics in all parts of the study, and we will be performing retrospective genomic tumor analysis at Ignyta's CAP CLIA lab.

Ignyta is relatively unique amongst therapeutically-focused biotech companies by having an in-house CAP CLIA diagnostic lab. This enables

us to fully integrate biomarker analysis into our development programs. For the entrectinib program, we have developed an RNA-based multiplex NGS assay called Trailblaze Pharos, which we perform to assess gene rearrangements, overexpression, insertions, deletions, and splice variants of NTRK1/2/3, ROS1, and ALK that are potentially relevant to our pediatric development plan.

For our pediatric program, this platform will be employed to help develop and guide a patient selection strategy which we would plan to carry into phase 1b and into future pediatric studies. For example, retrospective tumor genomic profiling will be conducted in all patients to assess if activating alterations such as TRKB overexpression predicts response.

Only in part D, which focuses on gene rearrangements, will testing be prospective and a condition for enrollment. However, this can be assessed by the Ignyta assay or by local methods such as Foundation Medicine or other clinical NGS assays.

But we can't find these patients alone. The incorporation of genomic profiling into routine clinical practice will be necessary if entrectinib and other targeted agents for these patient populations are to be successful. There are a number of private and public genomic profiling services that measure our targets, such as NTRK, ROS1, and ALK. So the infrastructure is being deployed.

However, it needs to be employed in the service of pediatric cancer patients in order to identify these patients who might benefit from these targeted approaches.

In summary, entrectinib is a potent inhibitor of TRK, ROS1, and ALK, and has demonstrated compelling preliminary efficacy against these targets and acceptable safety and tolerability in an adult patient population harboring gene rearrangements, including patients with CNS disease.

Based upon these adult clinical data, the fact that these same molecular alternations are

seen in pediatric tumors and with our preclinical models, together these provide strong rationale for pediatric development of entrectinib. We have, therefore, initiated the STARTRK Next-Generation study to explore this potential, and on the basis of this study, we are also seeking a written request.

Finally, let me conclude by saying we are eager to receive the advisory committee's feedback on our approach to pediatric development. Thank you.

DR. PAPPO: Thank you very much.

We will now take clarifying questions for the sponsor. Please remember to state your name for the record before you speak, and if you can, please direct questions to a specific presenter.

Dr. Weigel?

DR. WEIGEL: Hi. Brenda Weigel. Just for clarification and, also, a question. In your adult study, your recommended phase 2 dose was not actually the maximally tolerated dose, correct?

DR. MULTANI: Correct.

DR. WEIGEL: Can you walk us a little bit through the rationale of the selection of the adult recommended phase 2 dose and then how that has influenced your dosing levels in the pediatric phase 1 trial, because you are starting -- and I congratulate you on what you think is a biologically effective dose, which is fantastic, but then escalating considerably beyond that. Can you help us understand the rationale behind that and the questions being answered by doing that?

DR. MULTANI: Sure. Let me walk you through it. You can see how we picked the dose.

We initially dose escalated using a BSA-based dosing approach, so per meter squared. We went to 400 milligrams per meter squared and saw multiple examples of clinical activity with acceptable toxicity.

Our intent was to arrive at a fixed dose. So after 400 milligrams per meter squared, we stopped dose escalating on a per meter squared basis and transitioned to a fixed dose of 800 milligrams flat. It was at that point that we saw

our first two dose-limiting toxicities, one of which was a CNS toxicity, a patient who developed reversible confusion and gait instability. It was rapidly reversible, and dose reduction was employed.

However, we then backed down from 800 milligrams to 600 milligrams. We do think that that is the maximum tolerated dose in adults.

We have extensive PK now all the way from starting at 100 milligrams per meter squared up to 800 milligrams fixed. I can echo what was said previously that there is a loose but not tight correlation between exposure and response. We certainly feel very low exposures are not compellable response, but we have seen responses at the lower exposures.

We have carried the 600 milligrams forward, and, as I mentioned, we have treated, even in our phase 1 experience, 45 patients at this dose and continue to see a good safety profile, with additional evidence of activity.

It was based upon that adult PK data and

then the additional modeling that we did, as well as sort of understanding the IC90 that we are looking to clear, that we established our pediatric dosing regimen.

We wanted to start with a dose that was on a per meter squared basis lower than our adult dose to provide an initial margin as our first entry into children, but then we certainly would like to get to 400 milligrams per meter squared. That would be the intent. Then the protocol allows for further dose escalation, but it is not mandatory.

We do have PK that we are collecting, and then based upon refining our pediatric model and having an understanding of the exposures that we are achieving in the adult and the responses we are seeing in that setting, I think we could arrive at a pediatric dose that may not necessarily have to test dose-limiting toxicity.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you.

Dr. Seibel?

DR. SEIBEL: Thank you for your very

informative presentation.

Could you expand a bit more on the parathesias that you see?

DR. MULTANI: One of the toxicities that have been observed are peripheral parathesias. Sometimes they are oral. Sometimes they are in the periphery. Sometimes they are accompanied by dysgeusia, so altered taste. Readily reversible. Also, patients over time can become tolerant to them, as well.

In our higher exposure experiences, that has necessitated, in a few instances, dose reduction.

DR. SEIBEL: Any age correlation at all?

DR. MULTANI: Obviously, we are talking today about the challenges of going from infants to adolescents. In the adult setting, going from young adults to older adults, I can say that the CNS toxicity that we have observed often happens in patients who are in the older age bracket who are of low BSA, and not all cases, but often there is also concomitant opiate and medication that is also employed.

It is hard to pin a true relationship.

DR. SEIBEL: I think in your briefing document, you mentioned about the experience in patients who have had a previous TRK inhibitor and developed resistance to that and then they were treated with yours.

DR. MULTANI: We haven't treated enough --

DR. SEIBEL: Resistance?

DR. MULTANI: The two cases that were mentioned in the previous session were cases on our clinical trials. Two patients, one in the Italian study and one in the U.S. STARTRK-1 study, these were patients who initially responded and then developed resistance.

The Italian study, as I mentioned, initially explored intermittent dosing, and the first patient who developed resistance was on this intermittent dosing schedule of 4 days on, 3 days off with a week break with every cycle. So it was getting 12 days of drug out of every 28, and we felt that that was essentially a setup for driving resistance. That patient did develop resistance after cycle 4.

The second patient on the STARTRK-1 study, although she was on a continuous dosing regimen, she was developing parathesias which required dose reduction, and her exposures, she was at the low end of exposure in all of our experience. So she was essentially dropping below the IC90 and the IC50 on many occasions, and, again, that is sort of a setup for development of resistance.

DR. SEIBEL: I see. One last question then related to the ALK activity. I notice you just said ALK essentially translocations. You are not including patients who would have mutations, and what is the experience with the mutations, particularly the crizotinib-resistant mutations, what is the activity of that?

DR. MULTANI: This drug has been studied in patients who have developed regression post-crizotinib. We have not seen clinical activity in that setting.

We have seen, however, clinical activity in the setting of patients -- this is in the adult population -- patients who have

crizotinib-sensitive disease, but then progressed in the CNS, either ALK positive disease or ROS1-positive disease. We have been able to essentially arrest and, in some instances, reverse their CNS progression because of the ability of entrectinib to get into the brain, whereas crizotinib has more challenges.

On the pediatric side, our neuroblastoma cohort -- and perhaps I wasn't clear -- although it's testing the TRK hypothesis, we are prospectively enrolling all comers with neuroblastoma with the idea that retrospectively, we would try to analyze TRKB overexpression, what does that mean, and also try to get additional data in terms of ALK expression, ALK point mutations, which are also seen in that disease.

DR. SEIBEL: You showed that one slide with the NB-1 cell line, which is probably the one that people use for amplification. Do you have any other data to support the use of ALK inhibitor for amplification?

DR. MULTANI: We have the clinical example,

the patient in the Italian study who had an activating point mutation of ALK, 22-year-old woman.

DR. SEIBEL: But not amplification?

DR. MULTANI: She did not have amplification. It was an activating point mutation, yes.

DR. SEIBEL: Okay. Thank you.

DR. PAPPO: Thank you.

Dr. Warren?

DR. WARREN: Hi, Kathy Warren from NCI.

DR. MULTANI: Hello.

DR. WARREN: I have a question regarding your phase 1 study design. In the phase 1a, you define a maximum tolerated dose or a recommended phase 2 dose, and then it goes to 1b. For patients with CNS tumors, you drop a dose level.

My comment is I think that is too conservative, because in your table of adverse events, there was no headache. I don't think I have ever seen a phase 1 study in adults which didn't report headache as a common toxicity. No

evidence of increased intracranial pressure. No myelosuppression.

Those are the things that we would generally worry about in kids with CNS disease. Also, all of your adverse events are reversible, as you stated.

Our kids with recurrent progressive CNS tumors have really one good chance at an investigational agent at that time, and I think it would be prudent to give them the best opportunity to respond. So I don't understand why you drop a dose level. I would suggest expanding the cohort for CNS tumors.

Would you continue to dose escalate in that population if they tolerated that, the recommended phase 2 dose?

DR. MULTANI: We would.

DR. PAPPO: Thank you.

Dr. Raez?

DR. RAEZ: Elizabeth Raez. Thank you for your presentation.

I just had a question about the rationale for requiring a body surface area of at least 0.45

and if there were any plans to perhaps expand to younger patients.

DR. MULTANI: The study itself is open to age 2 and above, and we would potentially expand to a lower BSA compatible with that age range once we introduce the pediatric formulation. Since we are using capsules, we probably aren't going to be able to deliver it to that bracket there.

DR. RAEZ: Thanks.

DR. PAPPO: Thank you.

Steve?

DR. DUBOIS: Steve DuBois, Dana Farber. I wondered if you have treated any patients with inflammatory myofibroblastic tumors.

DR. MULTANI: We have not.

DR. DUBOIS: You have not. Then related to Dr. Seibel's question about the spectrum of activity of this agent, can you help us to understand the ALK inhibitory activity as it compares with ceritinib or lorlatinib, other agents that are being developed in pediatrics as ALK inhibitors?

DR. MULTANI: It is a potent ALK inhibitor, and it is essentially on par in potency with crizotinib. It does cross into the CNS like ceritinib. It is not active against the solvent front mutation that, for example, lorlatinib is active against.

DR. PAPPO: Thank you.

I had a couple of questions. There were, I think, 6 patients that came off study after achieving a response in that plot that you showed. Was that because of toxicity?

DR. MULTANI: Progression. We have not had a patient come off study in response for toxicity. Those were all progression events.

DR. PAPPO: Then the other question I had was the fact that there is no liquid formulation, that significantly affects the applicability of this drug to younger patients that have unique histologies, like infantile fibrosarcoma, et cetera. Is it just impossible to develop a liquid formulation, or are you still working on it?

DR. MULTANI: The actual sprinkle

formulation can be mixed with liquid and administered or in a very small volume of food. For example, the compassionate use case, the patient was 18 months old, and what we did there was just mix the contents of the capsule with the food. So that's the intent of how we could deliver to infants the pediatric formulation.

DR. PAPPO: Can you combine it just with water? Will it dissolve in water or no?

DR. MULTANI: It can be suspended in water.

DR. PAPPO: It can be suspended in water. Okay.

I think I had one more question, but since I'm not remembering, we'll move forward with Dr. Dunkel.

(Laughter.)

DR. DUNKEL: Ira Dunkel, Memorial Sloan Kettering. I wanted to hear a little bit more about the potential you think this has for the medulloblastoma, retinoblastoma, neuroblastoma patients who are overexpressed but don't have fusion or another mutation.

I think you gave us data from one preclinical model showing that, in principle, overexpression can be associated with efficacy.

DR. MULTANI: Right.

DR. DUNKEL: But I didn't know if that was one example of many and others failed or others also worked or if that is the only one that you have tested.

I was also wondering if you could tell us of these tumor types that have overexpression, how consistently the tumors have overexpression. Is it a small subset or a large subset or all of the patients overexpressed the TRK?

DR. MULTANI: Let me have Zac Hornby, our team leader for NTRK, to answer that question.

MR. HORNBY: Hello. Zac Hornby, team leader for NTRK.

We did indeed test four different TRKB overexpressed-driven models. They were, however, all models of neuroblastoma. We have not yet tested any preclinical models of either medulloblastoma or retinoblastoma.

In the literature, the same observation has been found of a correlation between TRKB overexpression and worse prognosis, but this would have to be tested empirically in the clinic.

DR. DUNKEL: I'm sorry. Can you also comment on the second part about do you know within those diseases how consistently they have the overexpression?

MR. HORNBY: I don't know the answer off the top of my head.

DR. MULTANI: I can say, though, that is why we are retrospectively collecting tissue to do a biomarker analysis, because even if there is -- to the degree that TRKB overexpression has been found in the literature, therapeutically, what the cutoff would be to define TRKB overexpression and what the methods used to make that determination still need to be determined.

There is a lot of retrospective biomarker activity that would be part of this and not just this study alone, but hopefully a follow-on study.

DR. PAPPO: Thank you.

Julia?

DR. GLADE BENDER: Thank you very much for your presentation.

I have a question about combinations. Given the fact that you have seen patients progress or develop resistance and you are going for diseases where we will definitely be using chemotherapy as part of our treatment regimens, can you comment on what combinations you have studied, what combinations you plan to study, and whether there is any evidence of synergy with any particular combination?

DR. MULTANI: The one combination that we have studied to date in neuroblastoma is the combination with topotecan and temozolomide.

We would expect that future development might involve combinations. We are set up for that, and once we get the pediatric study off the ground, we would entertain designs of how to then transition that to explore a combination approach.

DR. PAPPO: Thank you.

Dr. Warren?

DR. WARREN: Is there any correlation between your intratumoral TRK inhibition and your plasma exposure to the drug?

DR. MULTANI: We don't have that information.

DR. WARREN: But you have tumor tissue now, right, and you have blood?

DR. MULTANI: We do, but the tumor tissue that we get for diagnosis is pretreatment. We do have a few samples that are post-progression.

DR. PAPPO: Steve?

DR. DUBOIS: Just back to the biomarker question, how good is that assay for -- I presume it is immunohistochemistry for TRKB. To my knowledge, I imagine that is being done as a research assay, and maybe my panelists could help. But to my knowledge, I don't think that's being done in any clinical pathology labs for IHC.

I don't know if you can comment.

DR. MULTANI: We have both an IHC approach, as well as a RNA-based expression approach.

DR. DUBOIS: Then your performance

characteristics of the IHC, is it pretty clean?

DR. MULTANI: We have worked hard to essentially develop a TRK antibody that would be useful.

DR. PAPPO: Thank you.

Dr. MacDonald?

DR. MacDONALD: Tobey MacDonald. Perhaps you can clarify exactly at what point and where is TRK overexpression being evaluated in terms of at diagnosis, at relapse?

DR. MULTANI: At diagnosis.

DR. MacDONALD: Because unlike a gene rearrangement, we would expect TRK expression to be variable dependent upon treatments given. So your TRK expression at diagnosis may not be --

DR. MULTANI: We are trying to get the most recent specimen, but we understand that it may be at diagnosis.

DR. MacDONALD: Who would do the expression analysis, because that wouldn't be a routine? Even if we do molecular profiling, we wouldn't be looking at TRK.

DR. MULTANI: We would do that in our lab retrospectively is how it is currently defined.

DR. MacDONALD: Okay. It is just, obviously, you have many trials and you have many different targets and you also have research institutions. Just trying to logistically put it into my head when you have a relapsed tumor, why would this one get selected to send the tissue up to you rather than have an in-house screening approach which would be more favorable so we could select who most appropriately we should send out?

DR. MULTANI: I think once we can develop methods that we think are reproducible, they could then be transferred out.

DR. MacDONALD: Then finally, just a comment. I know about expression, traditionally, historically, TRKC expression actually in medulloblastoma has been associated with a favorable prognosis, not unfavorable. So I am not sure how you address that.

DR. MULTANI: That is not a core patient population within this study, but the study has

broad eligibility. We are, however, focusing on TRKB in neuroblastoma in the Phase 1/1b study, as well as the gene rearrangements.

DR. MacDONALD: Thank you.

DR. PAPPO: Thank you.

Dr. Reaman?

DR. REAMAN: Can you just clarify the current sprinkle formulation, it is just the same contents of the capsule, or are they different? Are there bioavailability studies that you have done sprinkling that on food, and how has that been assessed?

DR. MULTANI: So it is not just the capsule contents. It has been formulated to taste mask and be able to be sprinkled on food and have at least release characteristics that right now are compatible with dosing. Then we would expect to, before introducing it into the clinic, do a healthy volunteer bioavailability study.

DR. PAPPO: Dr. Brown?

DR. BROWN: I wanted to go back to the patients who responded and then progressed. Do you

have any insights on mechanisms of resistance in those patients?

DR. MULTANI: Just the two that have been mentioned where we were able to get post-progression biopsies and demonstrate presence of a resistant point mutation.

DR. BROWN: It wasn't that the other three were tested and were negative. It is just that they weren't tested.

DR. MULTANI: Correct.

DR. BROWN: Thank you.

DR. PAPPO: Any additional questions?

(No response.)

Open Public Hearing

DR. PAPPO: Thank you very much.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if you know, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance to the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issue before them. That said, in many instances and for many topics, there will be a variety of

opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson.

Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you represent for the record.

DR. GOSHOCK: Hi. Thank you for the opportunity to speak here today. My name is Dr. Laura Goshock, and I received my PhD from Johns Hopkins School of Medicine. Today I'm presenting comments on behalf of the National Center for Health Research.

Our research center scrutinizes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from pharmaceutical companies, and therefore, I have no

conflicts of interest.

The passage of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act has resulted in labeling changes for hundreds of drugs so that they may be used in pediatric populations. However, despite the success and advances in both basic science and clinical trials in pediatrics, off-label drug use in children and adolescents remains a problem. Moreover, off-label use of drugs presents an ever larger and more complex issue for children with chronic and/or rare diseases, like the cancers discussed here.

That's why we strongly support FDA advisory committee meetings such as this one to garner input from experts on how best to conduct clinical trials in pediatric patients. The panel has done a great job in asking specific questions to the drug sponsors about their trial design while offering helpful suggestions and input when needed.

However, despite the extraordinarily rare populations of patients to test these drugs, the scientific integrity of these trials needs to be

kept in mind when moving forward. When possible, randomized or well-matched control group or comparison samples for new drugs should be used because it is the ethical and scientifically valid design for proving whether a product is safe and effective.

During the analysis of the proposed clinical trials, also keep in mind the possible pitfalls associated with using surrogate endpoints in lieu of overall survival. A study published last year looked at cancer drugs approved over five years using surrogate endpoints.

In postmarket studies, only 14 percent of these approved cancer drugs were found to improve patient survival, and yet, our center found that all of the unproven cancer drugs were still on the market, many costing more than $100,000 a year.

These results show that surrogate endpoints such as objective response rate too often provide false hope when costing patients more than they can afford.

Additionally, as discussed with several of

the drugs, there are clearly subpopulations of patients who respond better to treatment than others. We encourage the sponsors to further characterize these positive responders in hopes of targeting the population of patients who would benefit the most from their treatment.

In conclusion, we realize that all five of the drugs discussed at this meeting are for treating very rare pediatric cancers that desperately need new treatments. For that very reason, if approved, these drugs may be tempting to use off label in pediatric patients.

Therefore, we commend the FDA and the panel for providing an open discussion on the best way in which to test these five new drugs in pediatric populations. This is a step in the right direction to help ensure that drugs are safe and effective for everyone who they are prescribed.

Thank you for your time.

Questions to the Subcommittee and Discussion

DR. PAPPO: Thank you.

The open public hearing portion of this

meeting has now concluded, and we will no longer take comments from the audience.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with the questions to the committee and panel discussions.

I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We will go ahead and start with question number 1.

DR. ERSHLER: 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.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open the question for discussion.

Steve?

DR. DUBOIS: I asked the question about inflammatory myofibroblastic tumor because I think, to my knowledge, that would be the only pediatric tumor that has a ROS-1 aberration. So I think that would be, in terms of ROS1, the one histology I can think of.

DR. PAPPO: Any comments on the overexpression of NTRK1/2 or ALK? I think that is not whether this agent will act in cases where these are overexpressed versus rearranged or ALK mutations, but I would like to hear your suggestions or comments.

Dr. Brown?

DR. BROWN: It wasn't about that, but for ROS1, I believe the 119 translocated to AOL has been demonstrated to overexpress ROS1 and also be sensitive to ROS1 inhibition in preclinical models, just something to mention.

DR. PAPPO: I believe that the company is going to be testing the -- they are going to be able to correlate overexpression of NTRK or ALK with response, and I guess we will have those

results at some point. But prospectively, I do not know that there is a correlation, and I cannot predict if there is going to be activity of this agent with tumors that overexpress these genes.

Steve?

DR. DUBOIS: Just to comment on the NANT trial of lestaurtinib, which is not a particularly potent TRK inhibitor nor particularly selective TRK inhibitor, but it is unusual with a single agent biologic to see any objective responses on some of those NANT trials which tend to enroll very heavily pretreated patients. So the fact that they observed 2 responses I think is perhaps reassuring that with more selective TRK inhibitors and more potent TRK inhibitors that there may be a role in neuroblastoma.

DR. PAPPO: These are patients with overexpression of NTRK or mutations?

DR. DUBOIS: They weren't selected. They were just relapse, refractory, no.

DR. PAPPO: Yes, Julia and then Nita.

DR. GLADE BENDER: I just wanted to

reiterate what Dr. MacDonald said about expression profiling. I think going on expression on archival tissue may not be appropriate. We will have to see. I think the rearrangements are pretty clear, but not the expression level on archival specimens.

DR. PAPPO: Nita?

DR. SEIBEL: I think we don't know particularly for ROS1 and the ALK amplification versus mutation. I think it is really important or essential that we capture those data. So I think we need to be able to make those correlations because right now, I think there is some presumption that these patients should be treated with an ALK inhibitor if they have an amplification.

The other thing is we have to work with the tissue that is available. Ideally, we'd like to have tissue from the most recent recurrence, but that is not possible. So I think we need the data for these to really get a background wherever we can get the tissue from initially.

DR. PAPPO: Any other comments or questions

regarding this question?

Yes, Brenda?

DR. WEIGEL: I think just echoing that, I would be very supportive and encouraging of continuing to collect as much data as possible to be able to answer some of these questions in a prospective manner. Even if it may not be the optimal tissue, it may at least give us a clue as to whether further studies are even indicated. So I would support encouraging that.

DR. PAPPO: Dr. Armstrong?

DR. ARMSTRONG: I will point out that in adult tumors when you make biopsy mandatory, more than 50 percent of the eligible patients don't go on trial. So it is a common issue, but particularly for these rare cancers, I would not make it mandatory. I think use what you have.

DR. PAPPO: Thank you.

Any additional comments or questions?

(No response.)

DR. PAPPO: I guess this trial would offer the opportunity to capture data to actually answer

this question, whether overexpression of some of these genes are appropriate biological targets for inhibition by entrectinib, and there might be a role for a very small subset of pediatric tumors in which ROS1 is rearranged, such as IMT or a subset of patients with leukemia in which this agent might prove useful.

Does that pretty much capture what everybody said?

(No response.)

DR. PAPPO: Okay. We will move to question number 2.

DR. ERSHLER: Please comment on the clinical availability and feasibility of NTRK1/2/3 and ROS-1 evaluation in current pediatric oncology practice.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open the question for discussion.

Yes, Dr. MacDonald?

DR. MacDONALD: I still think the TRK overexpression is going to be a little bit tricky as opposed to the rearrangements, particularly if

you talk about brain tumors. It's expressed in the brain. Who is determining what overexpression is in the brain? Are we comparing it to normal brain tissue? Whose estimate is it in the end, and who does it?

We don't routinely do that. You would have to have already in place a plan for that protocol specific to be looking at it. We are not going to screen, I don't think, every kiddo for TRK expression. It doesn't rise to the level of -- I still think that needs to be addressed in a thoughtful manner of how exactly the centers are going to look at that.

DR. PAPPO: I think regarding the availability and feasibility to test for this, it could be similar to the comment that Greg made in the previous presentation. It might be histology specific. If you have a tumor in which you suspect that there is going to be an aberration and if there are genes, it is worthwhile proceeding with extensive genomic testing to see if those patients could potentially benefit from this agent.

Any other comments or questions regarding this question?

Julia?

DR. GLADE BENDER: The other point I wanted to make was that I think in the clinical trial design, you mentioned that outside testing and programs, for example, who are doing comprehensive molecular profiling of tumors would be adequate testing to enter into the trial, but I think it would be very important for the study, if possible, to get tissues from those same patients to validate the testing from the outside source.

DR. PAPPO: Any other questions?

(No response.)

DR. PAPPO: To summarize, it might be difficult to evaluate TRK expression, but particularly in brain tumors. The second thing would be to take this availability and feasibility of evaluation of NTRK aberrations and ROS and ALK within the context of a specific histology, and if possible, it would be helpful to try to validate the studies that are done outside of your company

with tissue being actually validated at your company to be sure that the rearrangement or the mutation or whatever was really present.

Is that fair?

DR. GLADE BENDER: Expression, I think it's really the expression.

DR. PAPPO: Expression.

DR. GLADE BENDER: That data that would be interesting to validate across testing.

DR. PAPPO: Thank you.

We will move to question number 3.

DR. ERSHLER: Please consider the ongoing pediatric study and discuss the overall study design.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open the question for discussion.

Brenda?

DR. WEIGEL: Kathy and I are looking at each other because we both probably have comments.

I appreciate the design and starting at what we think is an effective dose. I would encourage

very careful consideration of the dose escalation, especially if toxicity does not end up being an endpoint in what the criteria are for defining the optimal dose, because I think that's not entirely clear in comparison to the adult dose.

I will leave the second comment to Kathy.

DR. WARREN: Actually, I was going to go back to the previous comments about mandatory biopsy. I think in general as we embark on precision medicine clinical trial, it is imperative for us to know whether the target is there that we are aiming for, and if we do not know if the sample tissue sample from diagnosis changed over time, then we should obtain tissue prior to going on an investigational trial that targets a specific thing.

DR. PAPPO: Thank you.

Yes, Brenda?

DR. WEIGEL: Then I would add, in addition, given that we are trying to potentially target CNS tumor patients, to echo Kathy's comment from before, that consideration of concurrent dosing for

the CNS patients and not de-escalating them a priori would be advisable and then continue to escalate as necessary based on toxicity and effect.

DR. PAPPO: Any additional comments or questions?

(No response.)

DR. PAPPO: One of the points would be to consider dose escalation, extra CNS and CNS tumors at the same time and not to de-escalate when you have a primary CNS tumor, the issue of considering mandatory biopsy at the time of recurrence to try to increase or at least try to validate the target for this specific agent, and encourage the issue of dose escalation.

I didn't understand if we should encourage it or discourage it. If you have achieved your optimal --

DR. WEIGEL: I think encourage it to achieve optimal biologic dose which may not mean escalating to maximally tolerated dose.

DR. PAPPO: Okay. Yes.

DR. GLADE BENDER: I just wanted to add to

Kathy's comment and ask a question of all of these studies in general. We require that there be measurable disease in order to enter on to certain trials, but certainly, I would think for brain tumors, there is often a reason to re-resect.

So I would ask if it were possible, maybe to consider a way to be able to have the re-resection specimen be the diagnostic biopsy, if you will, and then allow patients who have no evidence of disease to go on trial.

DR. PAPPO: Very good point.

Nita?

DR. SEIBEL: You used the term "mandatory biopsy at the time of recurrence," I think, in your summary. I guess I don't know if you can really use that. Strongly suggest, but yes.

DR. PAPPO: Encourage biopsy or re-biopsy at the time of recurrence.

DR. SEIBEL: Right, right.

DR. PAPPO: However, that is what we keep saying, and we don't do it, right?

DR. SEIBEL: You can't mandate that.

DR. WARREN: Just to follow up, when you don't make pharmacokinetic sampling mandatory, you get less than 50 percent participation on phase 1 trials. So I think in order to participate on a trial like this, unless you have a separate arm like potentially DIPG -- but I guess that is an afternoon discussion -- then I think we should do it.

DR. SEIBEL: We will exclude patients then.

DR. WARREN: Answer the question.

DR. SEIBEL: This is a broader discussion, but I don't think -- you have to take into account the risk and the benefit.

DR. PAPPO: Dr. Reaman?

DR. REAMAN: I think it depends to some extent on the objective of the study. It is hard to imagine that you could have a biologic rationale for enrolling a patient is that their tumor has the target that is being inhibited, but you have no knowledge of that a priori. It is a real question as to what the prospect for clinical benefit is for that patient.

I think I'm not sure that we can use the word "mandatory," but I think in some situations, something a little bit stronger than "strongly recommended" might be necessary.

DR. SEIBEL: But you have to have tissue to demonstrate the target.

DR. REAMAN: Right, right.

DR. SEIBEL: It's more the timing. Right.

DR. PAPPO: There are certain things that are not going to change.

DR. REAMAN: If you have archival tissue that demonstrates the target, that's fine, but I think that's the issue or the point that I was trying to make.

DR. PAPPO: There are certain things that are not going to change at the time of recurrence. The NTRK fusion is not going to change. So if you have archival tissue, that's okay.

But if you have a patient with neuroblastoma, you want to give them a RAS pathway inhibitor, and you know that 70 percent of neuroblastomas come back with a RAS mutation, then

you are going to have to biopsy that. I think it is a whole range of things.

DR. SEIBEL: Right, and we will find out more about that as things proceed.

DR. PAPPO: Correct, correct.

DR. SEIBEL: How many mutations develop from the time of diagnosis versus recurrence or multiple recurrence?

DR. PAPPO: Okay.

DR. NEVILLE: I was just going to say with some of the other trials, how we have handled it is that the biopsy is done if it is standard of care, and I would argue that, like Greg said, with the advent of biologics, even if it is an experimental drug, if you are going to treat someone with a biologic, you can argue it is standard of care.

The other thing is it depends on the risk-benefit of the biopsy, right? So there will be some kids who the recovery or the risk will be too great, and then maybe they are not eligible.

DR. PAPPO: Thank you.

Did you get all that? I don't have to

summarize that, right? That was a lot of back-and-forth.

(Laughter.)

DR. PAPPO: I don't want to say "mandatory" again.

Now, we will move to question number 3.

DR. ERSHLER: 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.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open the question for discussion.

Steve?

DR. DUBOIS: Just the experience in children receiving long-term crizotinib therapy has been a signal of renal toxicity, and it's not clear to me and I don't know if it is clear to anyone the mechanism of that. But if that is in some way due to an on-target ALK or ROS1 effect of crizotinib,

then that would certainly be something relevant to be monitored in this setting as well.

DR. PAPPO: Anybody else?

Yes, Ms. Haylock?

MS. HAYLOCK: In this setting, how are you defining long-term effects, because right now, long-term effects are decades later and a lot of these or most aren't going to survive that long? So are we talking a couple of years is a long-term effect or longer?

I think with a lot of these medications, I am not sure we really have any clue what the long-term effects are if these people survive to adulthood.

DR. PAPPO: I will try to tackle that, and then I will be happy for you all to add on or say I was wrong.

I think that there might be a subset of patients here that actually could survive long-term. If you have a patient with infantile fibrosarcoma in which you are able to resect the lesion with negative margins, it will be very

likely that it will not come back.

I don't know that we know a lot about the long-term effects of the inibs. It is a relatively new era since the 2000s when we started with Gleevec. So that is really not long-term follow-up, and I think that as we study this group of survivors, it is going to be a whole new generation of side effects that we are unaware of.

We are going to have to be very, very vigilant about some of these things, just like Steve mentioned about the renal toxicity.

I think, also, that we need to be extremely vigilant about the neurocognitive effects and the developmental effects of this drug, especially in the younger group of patients with a high rate of CNS penetration of this, and I assume that that is being prospectively collected in the protocol.

Greg?

DR. REAMAN: I would say I think the question was really designed for consideration of monitoring rather than mitigation of toxicities. I think the question was also designed to think about

if the drug does have activity, if the drug ends up being approved, if the drug does enter clinical practice, what can we think about monitoring as far as long-term potential toxicity.

It is not the immediate patient population that is enrolling on early phase studies, with rare exception, like Dr. Pappo mentioned, but it is really what kind of things should we be thinking about now, as everyone thinks targeted drugs are great because they are so nontoxic.

But as it turns out, they are toxic. They just have different types of toxicities. So that was really the intent of the question.

DR. PAPPO: Anybody else?

(No response.)

DR. PAPPO: I think that the best way to summarize this is that we have to be vigilant about the long-term toxicities. There might be some off-target effects that we are not aware of, and we just need to be very aware if this moves forward. And we have long-term survivors to monitor different toxicities other than just what we would

expect. For example, the renal toxicity example that you gave, Steve.

Question number 5.

DR. ERSHLER: Please address whether evaluation of this drug in pediatrics would require international collaboration.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open the question for discussion.

DR. REAMAN: I think we covered this probably sufficiently in all of our previous discussions. Rare tumors, small populations, the only way to overcome that challenge is to collaborate, collaborate, collaborate.

DR. PAPPO: Yes, Julie?

DR. GLADE BENDER: Although the neuroblastoma question may be able to be answered more swiftly here without an international collaboration.

DR. PAPPO: Ira?

DR. DUNKEL: This is a little bit maybe tangential to the question, but I am wondering for

the ultra-rare patients that we are talking about today, not the neuroblastoma, but the TRK fusions, now we are talking about two companies, two trials that compete for the same patients. What are the implications of having more than one agent even for international collaboration for an extremely rare population?

DR. PAPPO: Good point. If anybody wants to tackle that one?

Dr. Reaman?

(Laughter.)

DR. REAMAN: Isn't it a wonderful situation to be in? Have we ever been in this situation before? I think it is something that we will have to address as these studies progress and as development progresses as we learn more about each of these products.

I don't think there is any way to prospectively prioritize, predict at this time, and we are certainly not in a position to do so. But I think it will all play out, and I think we have heard the phrase before, "If you build it, they

will come."

We never thought that there would be patients enrolling on trials of gastrointestinal stromal tumors, and, sure enough, they were. So we will just see what happens.

DR. PAPPO: Brenda?

DR. WEIGEL: Brenda Weigel. I would just like to add a couple comments of support and echo what Dr. Reaman said. But I think what we have heard about these two agents is they are not identical. The first agent is a much more selective TRK inhibitor, if I have understood what the presentation involved, and then this one has additional ALK targeting and CNS differences, I think.

They may be different, and they both may have a place, depending on the patient population. I think we just don't know. And I think at this point in time, to limit our options would be not prudent, that it is worth exploring both, because I think they are fundamentally different drugs and we need to learn.

I think the patient population, especially if we think internationally, is there and it doesn't take very many patients if we hit some pretty big targets. I think I would very much encourage keeping all our options on the table, because I don't think they are identical drugs and we have a lot to learn.

DR. PAPPO: Thank you very much.

Any other comments?

(No response.)

DR. PAPPO: This will be a bullet summary. Bullet number 1, yes to international collaboration. Bullet number 2, neuroblastoma may be not needed for international collaboration. Bullet number 3, worth pursuing all these agents and all these drugs, because they might have different indications for select populations of patients.

Now we will go to question number 6.

DR. ERSHLER: Please comment on the adequacy of the current pediatric formulation and any future plans for the pediatric formulation.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open the question for discussion.

Steve and then Brenda.

DR. DUBOIS: I will just point out that there is compassionate use experience using the capsules opened and sprinkled on food, and might encourage the sponsor to think about not delaying evaluation in younger patients until their granule formulation is available. We have a track record of doing that, for example, with pediatric development of sunitinib.

DR. WEIGEL: I would encourage, as the sprinkle formulation is developed, to very carefully try to standardize that, look at solubility, binding to plastics, and really ensure equivalent bioavailability, if at all possible, to the delivery of both potentially the opened capsules and try to optimize that as much as you can, as it sounds like solubility is a big issue.

DR. PAPPO: Yes, Dr. Reaman?

DR. REAMAN: I would just caution with the

extemporaneous compounding of opening capsules, sprinkling on food, making sure that what food it gets sprinkled on doesn't interfere with bioavailability. If this is medication that is going to be administered at home, that there are appropriate instructions to parents, caregivers, about opening capsules, sprinkling on food, and what to do with leftover capsules' contents.

DR. PAPPO: Thank you.

Dr. Neville?

DR. NEVILLE: Just to echo and build on what Dr. Reaman said -- Kathleen Neville. I would encourage the sponsor to really get going on the bioavailability studies because you are sprinkling on food, and we don't know between suspension and food, food, no food, different foods, different juices.

We did some work where apple juice interfered with absorption, something you wouldn't expect. So I think before widespread use in that patient population, those studies need to be done.

DR. PAPPO: Any additional comment?

(No response.)

DR. PAPPO: We would encourage you to develop your granule formulation, and in the interim, when you do the capsules, to do bioavailability studies to try to optimize the use of this drug and to be better define what are the factors that may interfere with the bioavailability of the drug, like type of food, et cetera, et cetera.

Did I cover everything or do I need to say anything else?

(No response.)

Adjournment

DR. PAPPO: Be sure that adequate instructions are given to the family of how much to sprinkle, which foods to sprinkle it with, and what to do with the leftover medicine.

We will now break for lunch, and we will reconvene in this room at 1:00 p.m. Panel members, please remember that there should be no discussion of the meeting topic during lunch amongst yourselves or with any member of the audience.

Thank you.

(Whereupon, at 11:30 a.m., the morning session was adjourned.)