FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Tuesday, May 14, 2019

Morning Session

8:06 a.m. to 11:50 a.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

10903 New Hampshire Avenue

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

(8:06 a.m.)

Call to Order

Introduction of Committee

DR. RINI: Good morning everyone. Sorry for the tardiness. I'd like to remind everyone to please silence your cell phones, smartphones, or any other devices if you've not already done so. I'd also like to identify the FDA press contact, Amanda Turney.

Amanda, if you are present, please stand. Thank you.

My name is Brian Rini. I'm the chairperson for this meeting. I'll now call the morning session of today's meeting of the Oncologic Drugs Advisory Committee to order. We'll start by going around the table to introduce ourselves, and we'll start with the FDA to my left and go around the table.

DR. PAZDUR: Richard Pazdur, FDA.

DR. KEEGAN: Patricia Keegan, FDA.

DR. WARD: Ashley Ward, FDA.

DR. FASHOYIN-AJE: Lola Fashoyin-Aje, FDA.

DR. OSGOOD: Christy Osgood, FDA.

DR. FIERO: Mallorie Fiero, FDA.

DR. HUNSBERGER: Sally Hunsberger, NIH.

DR. HALABI: Susan Halabi, Duke University.

DR. CRISTOFANILLI: Massimo Cristofanilli, Northwestern University.

DR. ULDRICK: Thomas Uldrick, Fred Hutchinson Cancer Research Center.

DR. NOWAKOWSKI: Greg Nowakowski, Mayo Clinic, Rochester.

LCDR SHEPHERD: Jennifer Shepherd, designated federal officer, FDA.

DR. RINI: Brian Rini, Cleveland Clinic.

DR. KLEPIN: Heidi Klepin, Wake Forest.

DR. HOFFMAN: Philip Hoffman, University of Chicago.

MS. PREUSSE: Courtney Preusse, consumer rep.

MS. BROYLES: Susan Broyles, Aledo, Texas.

DR. WEINFURT: Kevin Weinfurt, Duke University.

DR. STRADER: Doris Strader, University of

Vermont.

DR. VILLALOBOS: Victor Villalobos, University of Colorado, Denver.

DR. CALIS: Karim Calis, NIH.

DR. MORROW: P.K. Morrow, Amgen.

DR. RINI: Thank you.

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 only 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 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 meeting topics during break or lunch. Thank you.

Now, I'll pass it to Lieutenant Commander Jennifer Shepherd, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

LCDR SHEPHERD: Good morning. The Food and Drug Administration is convening today's meeting of the Oncologic 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 affect 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 USC 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.

During the morning session, the committee will discuss the new drug application 211810, for pexidartinib capsules, submitted by Daiichi Sankyo, Incorporated. The proposed indication or use for this product is for the treatment of adult patients with symptomatic tenosynovial giant cell tumor, also referred to as giant cell tumor of the tendon sheath or pigmented villonodular synovitis, which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery.

This is a particular matters meeting during which specific matters related to Daiichi Sankyo's NDA will be discussed. Based on the agenda for

today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this 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 other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. RINI: We'll now proceed with FDA's introductory comments from Dr. Lola Fashoyin-Aje.

FDA Introductory Comments - Lola Fashoyin-Aje

DR. FASHOYIN-AJE: Members of the advisory committee, of the Daiichi Sankyo team, invited guests, visitors and FDA colleagues, good morning. My name is Lola Fashoyin-Aje. I'm a medical officer in the Office of Hematology and Oncology Products and the cross-discipline team leader for new drug application 211810.

Pexidartinib is an orally-administered, small-molecule, tyrosine kinase inhibitor of the colony-stimulating factor-1 receptor. Daiichi Sankyo seeks approval of pexidartinib for the treatment of adult patients with symptomatic tenosynovial giant cell tumor, which is associated with severe morbidity and functional limitations,

and which is not amenable to improvement with surgery.

As you will hear today, tenosynovial giant cell tumor, or TGCT, is a proliferative but rarely malignant disease. TGCT may manifest as one or more tumors that grow in extra-articular synovial tissues such as the tendon sheets or can be an intra-articular process involving the synovium and bursae.

The tumor mass typically expands in a slowly progressive or indolent manner, and patients typically experience symptoms such as pain, stiffness, swelling, or reduced range of motion, the severity of which depends on the size and the location of the tumor or tumors. TGCT can cause significant impairment and adversely affect how patients feel and function.

The spectrum of the therapeutic approaches to managing this disease ranges from observation with serial follow-up imaging and supportive measures to treat symptoms, to surgical interventions aimed to resect the tumor mass. In

patients for whom surgical excision of the tumor is feasible, this approach is often used. However, up to a third of patients experience tumor recurrence requiring additional surgical procedures, including in some cases joint replacement or amputation.

Beyond surgical interventions, radiation has been used in some cases, either alone or as an adjunctive therapy to surgical interventions, often with limited effectiveness. Notably however, there are no systemic therapies approved for the treatment of this disease, representing an unmet medical need for patients with TGCT who are not candidates for surgery or for whom surgical resection would be associated with excess morbidity.

Daiichi Sankyo's NDA dossier includes the results of the ENLIVEN trial to support the primary assessment of efficacy and safety of pexidartinib in the indicated population. This trial is a randomized, double-blind, placebo-controlled trial designed to assess the efficacy of pexidartinib as measured by the overall response rate at week 25 as

a primary efficacy endpoint and by patient and clinician reported clinical outcome assessment measures, also measured at week 25, as key secondary endpoints to evaluate the effects of pexidartinib on the physical and functional aspects of the disease.

This slide outlines the major review issues for this application with the assessment of the clinical benefit, and the assessment of an identified risk of liver injury in pexidartinib treated patients.

In the ENLIVEN trial, there was a statistically significant improvement in overall response rate in patients randomized to the pexidartinib arm compared to patients randomized to the placebo arm at the time of the primary analysis of overall response rate at week 25. A total of 23 patients randomized to pexidartinib experienced responses for an overall response rate or ORR, of 38 percent compared to no responses in patients randomized to placebo.

An analysis of duration of response based

upon additional follow-up, after the week 25 analysis of overall response rate, demonstrated that 22 of 23 responders experienced responses that were durable for 6 months or more, and that 13 of 13 responders who had been followed for a minimum of 12 months, following the initial response, maintained their responses at the 12-month post-response landmark.

Additionally, patients randomized to pexidartinib also demonstrated a statistically significant improvement in the key secondary clinical outcome assessment endpoints of mean change from baseline for range of motion, for physical function, and for worse stiffness, compared to patients randomized to placebo as shown in the first 3 rows on the table at the bottom of this slide.

As you will note, a large proportion of patients have missing clinical outcome assessment data ranging from 27 percent to 43 percent as shown in red.

In describing the assessment of clinical

benefit, the main review issue for the FDA is discerning whether the data package that supports this NDA provides robust evidence of clinical benefit in the context of a progressive, slow growing, and nonfatal disease that can cause significant functional impairment.

The FDA review team recognizes that assessing the treatment benefit of pexidartinib, based upon tumor burden reduction alone, may not be sufficient to fully characterize the effects of this drug as a potential treatment for TGCT given the features of the disease.

The design of the ENLIVEN trial allowed for an assessment of benefit that included measures of effects on tumor burden and measures of effects on the symptomatic and functional aspects of the disease.

FDA's assessment is that the results of the analysis of overall response rate, supported by the durability of the responses, demonstrate a favorable effect of pexidartinib on tumor burden. However, less clear is the effect of pexidartinib

on the functional and physical aspects of TGCT as measured in the ENLIVEN trial given the uncertainties in estimating effects on the clinical outcome assessment endpoints and in interpreting the clinical outcome assessment results, and given the high proportion of patients with missing assessment data and the amendments to the ENLIVEN trial to reorder the hierarchical testing of secondary endpoints to mitigate the impact of missing data.

Additional factors leading to uncertainties and interpretation of the clinical outcome assessment results include the potential unblinding of clinical assessors and establishing a clinically meaningful threshold of benefit. Dr. Fiero will describe these limitations and uncertainties in detail during the FDA presentation.

The risk of liver injury in patients who receive pexidartinib is also a major review issue. In the ENLIVEN trial, serum transaminase elevations occurred in a majority of patients. Elevations in alanine transaminase, or ALT, and aspartate

transaminase, or AST, occurred in 67 percent and 90 percent of patients, respectively. Bilirubin increases occurred less frequently in 12 percent of patients.

Importantly, approximately 5 percent of patients in the ENLIVEN trial experienced a pattern of serum transaminase and bilirubin elevation that is indicative of severe liver injury, characterized by AST or ALT greater than 3 times the upper limit of normal with concurrent bilirubin increases greater than 2 times the upper limit of normal. Across the development program, in patients with and without TGCT, a similar frequency and severity in serum transaminase and bilirubin abnormalities was observed.

Concerning in the context of a disease that is not life threatening was the observation of two cases of irreversible liver injury among the 768 patients in the overall development program for pexidartinib. One patient subsequently underwent liver transplantation and another died due to several factors, including liver failure.

In the few patients with evidence of severe liver injury whose workup included biopsies, including the aforementioned 2 patients, there was evidence of bile duct injury. Therefore, the spectrum of liver injury in pexidartinib treated patients ranges from serum transaminase and bilirubin elevation, to ductopenia, to liver failure.

This is what we know about the safety profile of pexidartinib, and Dr. Osgood will discuss these known risks and Daiichi Sankyo's proposed measures to mitigate them in her presentation.

There are also some uncertainties about the long-term effects of treatment with pexidartinib. Although the majority of patients who experienced serum transaminase and bilirubin elevations while receiving pexidartinib had improvement to baseline levels with dose reductions, dose interruptions, and/or discontinuation of pexidartinib, some patients, including 2 patients with TGCT, had a prolonged time to recovery despite implementation

of these measures.

Because serial biopsies were not performed in most patients with evidence of liver injury, the scope of the liver injury that may occur in the setting of clinically normal or improved serum transaminase and bilirubin levels is unknown. Furthermore, it is unclear whether pexidartinib causes subacute and/or chronic indolent injury, which is not detectable with laboratory monitoring but which may result in adverse clinical outcomes.

In summary, patients with TGCT may experience significant physical impairment, particularly when the disease is not amenable to surgical resection. There are no available systemic therapies for the treatment of these patients. Still, TGCT is not a fatal disease and that the balance of benefit and risk must be weighed differently than would be typically done for therapies indicated for the palliative treatment of life-threatening or fatal conditions.

For the first issue for discussion today, FDA considers robust anti-tumor effects supported

by equally robust effects on the clinical outcome assessment endpoints that are clinically relevant to patients with TGCT as important criteria to demonstrating clinical benefit in this disease.

The results of the ENLIVEN trial meet the first criterion. Whether the second criterion has been met is less clear, given the limitations in the estimation of effects on the clinical outcome assessment endpoints and in the interpretation of the clinical outcome assessment results.

To the second issue for discussion today, while the vast majority of patients who were randomized to the pexidartinib arm and who experienced serum transaminase and bilirubin elevations, had improvement to baseline values, with adequate monitoring of the relevant laboratory parameters and the implementation of dose modifications and withdrawal of the drug, some patients experienced severe liver injury despite these measures.

Additionally, there remain uncertainties regarding the long-term effects of this drug for

both injury that is identifiable with laboratory monitoring and injury that may be subclinical, progressive, and that may result in adverse outcomes.

The FDA review team seeks input from the advisory committee on whether the benefits of pexidartinib outweigh its risks in the proposed indication. This concludes my remarks. I thank you for your attention.

DR. RINI: Thank you.

Dr. Lewis, if you could just introduce yourself for the record into the microphone.

DR. LEWIS: My name is Val Lewis. I'm an orthopedic oncologist and professor and chair of orthopedics at MD Anderson Cancer Center, Houston, Texas.

DR. RINI: Thank you.

Both the FDA and 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 nonemployee 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 this 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, and we'll now proceed with the applicant's presentation.

Applicant Presentation - Eric Richards

MR. RICHARDS: Good morning, chairman, FDA, and members of the ODAC committee. My name is Eric Richards. I am the head of global regulatory affairs oncology at Daiichi Sankyo. On behalf of Daiichi Sankyo, I am pleased to be here today to

discuss the pexidartinib application.

Tenosynovial giant cell tumor, or TGCT, represents an unmet need. It is a rare, non-malignant tumor of the synovium that affects musculoskeletal joints. Symptoms include pain, stiffness, and functional impairment that can sometimes be severe.

Surgical resection is the primary treatment modality for the disease, but diffuse disease can be difficult to manage surgically. And for some patients, their disease may not be amenable to surgery due to significant surgical morbidity. Limb amputation may be required in severe and recurrent cases. There are no approved systemic therapies for this disease.

Pictured here are several extreme cases of TGCT, where the burden of disease is highest and clearly evident. This slide describes the pathophysiology of TGCT and the role of CSF-1. A genetic translocation leads to the overexpression of CSF-1, which controls various macrophage functions. This over expression of CSF-1 by

neoplastic cells leads to the recruitment of inflammatory non-neoplastic cells that from the tumor. The tumor primarily consists of mononuclear and multinucleated giant cells.

Inhibition of the CSF-1 receptor with pexidartinib blocks the autocrine loop that drives proliferation of neoplastic cells and the paracrine loop that recruits inflammatory cells, thereby leading to tumor regression.

Pexidartinib is a novel, highly selective, small molecule, tyrosine kinase inhibitor of the CSF-1 receptor. It also inhibits c-Kit and FLT3. The chi-no [ph] map on the right shows that it is highly selective for CSF-1R with an IC50 of 17 nanomolar in a cell-free assay.

Pexidartinib is orally bioavailable and has a half-life of 27 hours. It is predominantly metabolized in the liver by UGT1A4 and CYP3A, therefore, dose reductions are recommended for strong inhibitors of these isoenzymes. In subjects with renal impairment, there is 40 percent change in pexidartinib exposure. There was no observed

effect on mild hepatic impairment on exposure. Neither pexidartinib nor its major metabolite are associated with QTc prolongation.

The clinical evidence to support the proposed indication is derived from a phase 1 study involving 39 TGCT patients and a randomized double-blind phase 3 study in 61 patients treated with pexidartinib and 59 patients treated with placebo. The median duration of exposure to pexidartinib for TGCT patients was approximately 70 weeks with some patients exposed for 5 years.

In addition to the 130 TGCT patients treated with pexidartinib, there were 638 cancer patients treated with pexidartinib monotherapy or in combination with anticancer agents. Finally, an additional 30 patients were treated in a DDI study that enrolled TGCT and cancer patients. In total, 798 patients have been treated with pexidartinib over the clinical development program.

The proposed indication for pexidartinib is for the treatment of adult patients with symptomatic tenosynovial giant cell tumor, TGCT,

associated with severe morbidity or functional limitations and not amenable to improvement with surgery. This indication is intended to select a population with little to no options and for whom the benefit-risk profile is most positive. Pexidartinib is supplied in 200-milligram capsules and the proposed dosing regimen is 400 milligrams twice daily on an empty stomach.

Today you will hear about the high unmet medical need in TGCT where no approved systemic therapies exist and the important role that CSF-1 plays as a strong driver of the disease. We will describe the efficacy data for pexidartinib and how this clearly establishes the robust effect on tumor response and clinically meaningful improvement in functional and disease symptoms as measured by clinical and patient-reported outcomes.

We will discuss how the safety profile of pexidartinib has been well established and is generally manageable, and we will discuss in detail the serious cases of mixed or cholestatic hepatotoxicity that have been observed. We will

also describe our proposed risk mitigation measures, which include a risk evaluation and mitigation strategy and an associated patient registry.

Lastly, we will conclude that pexidartinib has a positive benefit-risk profile in the TGCT population with severe morbidity or functional limitation, and in whom the disease is not amenable to improvement with surgery.

The following is an outline of our presentation. Dr. Nicholas Bernthal, an orthopedic oncologists, will describe the disease and unmet need, followed by Dr. William Tap, the principal investigator of ENLIVEN, the phase 3 study, who will describe the efficacy data for pexidartinib and TGCT.

Dr. Antoine Yver of Daiichi Sankyo and Dr. Laurie DeLeve from USC will present the safety profile of pexidartinib. I will then come back to discuss the proposed risk evaluation and mitigation Strategy, and finally. Dr. William Tap will come back to share his clinical perspective on the

benefit-risk profile of pexidartinib in the intended population.

The following is a list of consultants that will be available to address, uh, questions regarding specific topics. I will now hand off to Dr [inaudible] who will walk us through the unmet need and burden of disease in TGCT.

Applicant Presentation - Nicholas Bernthal

DR. BERNTHAL: Good morning, and thank you for your time. My name is Nick Bernthal. I lead the musculoskeletal oncology section at UCLA. I'm a paid consultant of the sponsor but have no financial interest in the outcome of the meeting. Over the next few minutes, I'd like to give you a little bit of background on TGCT and the current treatment landscape from my perspective as a surgeon who treats patients.

TGCT is a non-malignant tumor of the synovium that affects the lining of a variety of joints. It typically affects patients in one joint and is often disfiguring. Disease is not fatal but causes significant morbidity leading to pain,

swelling, stiffness, and decreased functionality.

Importantly, TGCT affects people in the functional prime of their lives. These patients, often in their 20s and 30s, are being managed symptomatically often with long-term analgesics and opioids. By definition, TGCT is a synovial infiltrate with large amounts of hemosiderin deposition that's driven by CSF-1R. However, it's important to understand that the phenotype is separated into two very distinct clinical presentations.

On the left, localized TGCT is a well circumscribed, isolated nodule of disease that's easily resected with a straightforward, often outpatient surgery. On the right, diffuse TGCT is an infiltrative tumor representing an ill-defined aggressive synovial proliferation that erodes through tissue planes and anatomic boundaries.

In terms of epidemiology, the vast majority of patients presenting with TGCT have localized disease with more than a 10 to 1 predominance. This is critical given that most localized type

disease is treated with a simple surgical cure with little morbidity and low recurrence rates.

The localized TGCT population that can be cured by surgery are not the patient population we're discussing here today. Diffuse disease seen in fewer than 10 percent of TGCT patients is far more challenging for surgeons and patients alike. These patients are the focus of our talk today as they represent the current unmet need.

If you look here at the image on the left, this is a localized tumor type we talked about, a single nodule that would be removed simply with a surgical excision; whereas the center and right images are from a patient with diffuse disease. These represent the opposite end of the clinical spectrum of TGCT.

If you look at these images, you cannot overstate the destruction to the knee. Where the tumor ends and where normal tissue begins is virtually indistinguishable. The bone loss from the inflammation is clear. These are patients for whom our only option has been very aggressive

surgery, removing the entire synovium and surrounding tissue. And even with that, we still have more than 50 percent recurrence rates and persistent pain and morbidity. These patients often undergo multiple surgeries, often require joint replacement, and sometimes go on to amputation.

This is an example of one such patient, a young man I've treated over the last decade. He started in Boston with a biopsy and arthroscopic surgery at age 22. You see repeat arthroscopies until an open resection at age 25. At age 26, he goes on to get a total knee replacement, but even that doesn't solve his problem. It allows him to be ambulatory, but he continues to have recalcitrant pain, stiffness, and swelling.

Now look at this from the perspective of the impact on his life. This young man's life has been massively uprooted; leaves of absence from undergrad and law school; transferring jobs because he couldn't manage the swelling symptoms in cold climates; over 750 total days off for this patient

in the last 15 years. He's had regular physical therapy, dozens of braces, compression socks, and ice machines. The point is, is this is an absolutely life-altering disease when you have diffuse recalcitrant TGCT.

As a nonmalignant but highly morbid tumor, diffuse TGCT is difficult to characterize and requires non-traditional metrics. Even from a basic radiologic standpoint, these tumors are irregular in shape and non-spherical. To address this, we often add a volumetric measurement called tumor volume, TVS, which is calculated as a percentage of the entire synovium.

Unlike most tumors, the impact of TGCT is not measured in mortality; it's measured in functional disability. In order to assess this, we start with ubiquitous objective musculoskeletal metrics like range of motion measured by the physician with a goniometer. It's important to understand, though, that the clinical relevance of range of motion is highly joint dependent.

For example, a fused ankle with zero degrees

of motion can be a highly functional pain-free joint. For the knee, however, the most common joint affected by TGCT, range of motion is highly correlated with functional capacity. For example, a patient needs 65 degrees of flexion to walk on a level surface, approximately 80 degrees to go up and down stairs, 90 to get in and out of a chair, and 110 degrees to perform most activities of daily living.

Additionally, we adopted a patient-reported tool, the NIH-developed PROMIS Physical Function Score, a validated metric that evaluates overall musculoskeletal wellbeing. PROMIS PF is widely used in orthopedic conditions to assess disability and effectiveness of interventions and has the added benefit of being applicable to all joints.

To put the functionality of PROMIS-PF in context, the impact of two of the most effective orthopedic interventions are depicted here. Total shoulder replacement on the left and total knee replacement on the right are widely accepted life-improving interventions. When evaluated by

PROMIS-PF, recent publications showed that total shoulder replacement leads to a mean improvement of 3.7 points on a PROMIS scale, and total knee replacement leads to an 8.6 point improvement.

So now we return to this patient with recalcitrant diffuse type disease. In this case, we do a radical synovectomy of both the front and back of the knee joint. We replaced the distal femur and the entire knee joint, and yet the procedure is not the end of the road. The patient is now ambulatory but continues to have recurrent swelling, stiffness, and pain. His tumor burden is challenging to manage and his PROMIS scores remain low.

We know that these patients, despite being young and healthy otherwise, are at a significantly higher risk of infection, stiffness, and prolonged functional burden even after undergoing total joint replacement as compared to our typical patients.

Thus, nearly all localized TGCT patients and many diffuse TGCT patients can be cured with surgery, but those who cannot, fall into a clinical

no-man's land. They travel from physician to physician, from internal medicine, to sports medicine, to rheumatology, and then they often end up back with us, the orthopedic oncologist.

We are then stuck with a no-win proposition. We offer them pain medication for palliation, additional non-curative deforming surgery, or amputation. Given no medical options, patients usually choose the path of periodic trips to the operating room, whittling away at disease once the pain and disability reach an intolerable level, only knowing that this temporization is short-lived and highly morbid.

What pexidartinib offers is a paradigm shift for patients for whom surgery fails. While the patient journey previously ended with us, a targeted systemic drug effective against the most recalcitrant of cases allows us to create a patient-specific treatment pathway that leverages a multidisciplinary team. These patients for whom TGCT so drastically impacts the prime of their lives will now potentially have another option.

I would like to turn the presentation over to Dr. Bill Tap to discuss the clinical efficacy of pexidartinib.

Applicant Presentation - William Tap

DR. TAP: Thank you, Dr. Bernthal.

My name is William Tap. I am the chief of the medical oncology service, the sarcoma service at Memorial Sloan Kettering Cancer Center. I'm a paid consultant for Daiichi Sankyo, but I have no financial interest in the outcome of this meeting.

I have been fortunate to be involved with the development of pexidartinib since the phase 1 study. It is well established that CSF-1 signaling drives tumor formation in TGCT, so pexidartinib's mechanism of action, the targeting of CSF-1, makes sense in this disease.

I'd like to offer some more detail about our development program, our study design and rationale, and what we found as far as efficacy. The pexidartinib clinical development program consists of 159 TGCT patients. First, there was the phase 1 study that had an extension cohort that

included 39 patients with TGCT. This led to the phase 3 ENLIVEN study, which enrolled 120 patients with TGCT. This included 61 patients randomized to pexidartinib in part 1, as well as 30 who crossed over from placebo to pexidartinib in part 2. Our efficacy data in TGCT comes from a total of 130 patients who have received pexidartinib over the course of these two studies.

In the phase 1 study, dose escalation established 1,000 milligrams per day as the maximum tolerated dose. Dose-limiting toxicities included increased AST and bone marrow suppression. A thousand milligrams per day in divided doses was then evaluated in the phase 1 extension study. Thirty-nine patients were enrolled in the TGCT extension cohort and 20 where evaluable at the interim analysis, which is shown here. Sixty percent of evaluable patients had a partial response by RECIST. These promising results led to the development of the ENLIVEN study.

ENLIVEN was an adequate and well-controlled randomized, double-blind phase 3 study. We

enrolled patients who had histologically confirmed advance TGCT for whom surgical resection could potentially worsen functional limitation or cause severe morbidity. Patients were required to be symptomatic and have measurable disease of at least 2 centimeters by RECIST.

Randomization was stratified by U.S. versus non-U.S. sites and upper versus lower extremity disease. ENLIVEN was composed of two parts. Part 1 was 24 weeks. Patients were randomized in a 1 to 1 fashion to receive either pexidartinib or placebo. Pexidartinib was given at a thousand milligrams per day in split doses for 2 weeks. After 2 weeks, patients were dosed-reduced to 800 milligrams a day in split doses for 22 weeks. Overall, 120 patients with TGCT in part 1 were randomized and treated.

After the 25-week assessment, a patient could move into part 2 of the trial. This was an open-label extension in which all patients would receive pexidartinib at their part 1 dose. There were 30 patients who crossed over in this way. The

data cutoff for the primary analysis at week 25 was March of 2017. The data cutoff for the mature efficacy and safety results was January 31st of 2018.

The primary endpoint was overall response rate at week 25 based on blinded, central review of MRI scans using RECIST. Secondary endpoints included 5 prespecified comparative analyses at week 25; range of motion, as measured by a third party using goniometry assessments; overall response rate by tumor volume score; PROMIS Physical Function scale; worst stiffness; and pain inventory.

These tools have been validated in orthopedic populations, and FDA guidelines were followed for the TGCT population. Duration of response was also measured by RECIST and the tumor volume score, but it was not mature at week 25.

The study had a 90 percent power to detect a 25 percent difference in response rates, assuming an active response rate of 35 percent and a placebo response rate of 10 percent. This required a

sample size of 126 patients with a two-sided alpha of 0.05.

We observed 2 cases of cholestatic hepatotoxicity in ENLIVEN, so the data monitoring committee was requested to review unblinded safety data. The DMC recommended study changes, including an accrual stoppage. This occurred in September of 2016 when the majority of the study was already accrued. The study was held with 120 patients enrolled versus the target of 126.

Ongoing patients were allowed to continue if they so chose under reconsent. No new exposure to pexidartinib was allowed. Therefore, after completion of the end of part 1 assessments at week 25, patients who wished to continue were unblinded and patients on placebo were discontinued. After database lock and study unblinding, it was revealed that 30 patients had crossed over to pexidartinib before implementation of the DMC action. They continued on therapy.

In part 1, 61 patients were randomized to pexidartinib and 59 patients to matching placebo.

Fifteen percent on the pexidartinib arm discontinued early as compared to 19 percent on placebo. The most common reason for discontinuation on pexidartinib was an adverse event, while withdrawal of consent was the most common reason on placebo.

Demographics in the intention-to-treat population were balanced between treatment groups. There was a slight preponderance of females in both arms. This is expected given that TGCT is more common in females. The knee was the most common location of disease.

About half of the patients in both arms had prior surgery and most had not received prior systemic therapy. The majority had used prior analgesics. To be eligible for the study, qualified personnel, for example, 2 surgeons or a multidisciplinary tumor board, had to determine that surgical resection would be associated with potentially worsening function or severe morbidity. Nearly all subjects how a moderate or severe risk of surgical morbidity.

If we look at the baseline characteristics, there were no notable differences between the two groups. Range of motion and PROMIS Physical Function score, as well as worst stiffness and pain, were similar across both groups.

Pexidartinib met its primary endpoint in ENLIVEN. The overall response rate at week 25 by blinded central review demonstrates a significant difference between pexidartinib and placebo. Based on RECIST, 9 patients on pexidartinib had a complete response; 15 a partial response; and 24 stable disease. This resulted in an overall response rate of 39 percent for pexidartinib at week 25 compared to zero percent for placebo. This was highly statistically significant.

We also observed a statistically significant and clinically meaningful improvement in the first 4 secondary endpoints. This included the objective measures, range of motion and overall response rate by tumor volume score and patient-reported outcomes, PROMIS Physical Function, and worst stiffness. Importantly, these improvements are

substantial. For example, as Dr. Bernthal explained, a 4-point improvement in the PROMIS Physical Function score is in the range that should be achieved with certain joint replacements.

A number of subjects were missing valid end of part 1 week 25 PRO assessments. The primary reasons were early discontinuation in about 17 percent of patients and protocol non-compliance or technical problems with the electronic diary in 24 percent of patients.

To help address the impact of this missing data, BPI 30 pain responder, which was most impacted, was moved to the bottom of the secondary endpoint analysis, and range of motion endpoint was analyzed first. The change to the secondary endpoint hierarchy was made in consultation with the FDA and by protocol amendment prior to database lock at unblinding. There were additional exploratory and sensitivity analyses planned to assess the impact of the missing data on these endpoints.

At the request of the agency, we conducted a

sensitivity analysis to assess the impact of the missing PRO data. This analysis included all patients who had a valid baseline and at least one post baseline assessment. The mixed-model repeated measures analyses showed clinically meaningful results across all measured and points, including worst pain. Additional post hoc sensitivity analyses support positive efficacy outcomes, even if the data were not missing at random.

Now that I've taken you through part 1 and demonstrated that pexidartinib is effective, I'd like to move on to present part 2, which shows that efficacy is durable. Recall that these more mature results include the 30 additional patients who crossed over to pexidartinib after part 1, all at the proposed dose of 800 milligrams per day.

Using the January 2018 data cutoff, we have 3 TGCT cohorts: the randomized ENLIVEN cohort, the crossover of 30 patients, and the matured results from the phase 1 study. Median treatment duration is 17 months, so these data are mature.

These data show us that prolonged treatment

provides progressive tumor reduction. The best overall RECIST response rate for the randomized cohort is higher than the response rate at week 25, 53 percent versus 39 percent. Best overall response rate is very consistent across all three cohorts, and as you can see, duration of response is very long with few subjects experiencing progressive disease.

Here we have plotted the time to response Kaplan-Meier curve for the 91 TGCT patients in ENLIVEN. Continued responses are noted with time. We also plotted a Kaplan-Meier curve for the duration of response, which shows that the treatment effect persists. These data support continued treatment with pexidartinib.

The vast majority of patients experienced tumor reduction with pexidartinib. This waterfall plot of tumor volume shows that 64 percent had a TVS response defined as greater than or equal to a 50 percent decrease in tumor volume score. This is what we expect to see based on the biomarker data showing that CSF-1 is the primary driver of this

disease.

In conclusion, pexidartinib was associated with a very clear and durable benefit among patients with TGCT. ENLIVEN met its primary of overall response rate by RECIST at week 25. This was supported by consistent benefit across cohorts as well as secondary endpoints measuring function and symptomatic improvement. The benefits observed with pexidartinib were durable and clinically meaningful for the patient.

I will now hand over the presentation to Dr. Antoine Yver, who will discuss the general safety results for pexidartinib.

Applicant Presentation - Antoine Yver

DR. YVER: Thank you, Dr. Tap.

My name is Antoine Yver. I'm the global head of oncology, representing the development of Daiichi Sankyo. Now that you've seen the comparing clinical benefit of pexidartinib in this disease, I will describe the general safety profile of pexidartinib.

Our primary assessment of safety in the TGCT

population comes from the part 1 randomized placebo-controlled comparison in ENLIVEN, which represents the first 25 weeks on study. During the randomized portion of the study, patients were treated for a mean of about 22 weeks in both groups. Almost all patients had at least one adverse event, and there were more grade 3 or 4 adverse events and serious AEs in the pexidartinib group.

Thirteen percent of patients in the pexidartinib group experienced an AE [indiscernible] with discontinuation compared with none in the placebo group. Thirty-eight percent of patients in the pexidartinib group had an adverse event associated with dose interruption or dose reduction versus 10 percent in the placebo group.

Most frequently reported treatment-emergent adverse events are shown here. The blue bars to the left represent the pexidartinib and grade 3 or 4 AEs are indicated with a darker shade. Adverse events were more frequent in the pexidartinib group, so most common events were hair color

changes, nausea, fatigue, and liver enzyme increases.

As we can see, the vast majority of AEs on pexidartinib and placebo were grade 1 or 2 in severity. Keen reaction like rash and hair color changes to gray or white are expected based on pexidartinib's targeting of c-Kit. Liver enzyme abnormalities, particularly AST and ALT increases, are consistent with the mechanism of CSF-1 receptor inhibition. This will be discussed later.

Overall, this AE profile is expected based on the mechanism of action for pexidartinib. Please keep in mind that these events were reversible.

As I mentioned, 8 patients in the pexidartinib group discontinued study drug due to adverse events; 7 out of these 8 subjects discontinued due to liver related adverse event. Only 6 patients had a dose interruption reduction in the placebo group compared with 23 patients in the pexidartinib group.

The majority of dose modifications in the

pexidartinib groups were due to liver enzyme elevation, mostly AST or ALT increases and gastrointestinal disorders, such as nausea and vomiting. Of these 23 subjects, all were able to continue on pexidartinib treatment after initial dose changes. Only 6 of them later discontinued due to AEs. We looked at a number of variables and found no predictive factors for AE leading to dose interruption or reduction.

Here we're looking at long-term safety through January 2018, which was the cutoff for the submission. On the left is a cohort of 61 patients treated with pexidartinib in a randomized phase of ENLIVEN, then we have 30 patients from ENLIVEN open-label crossover cohort, and on the right are the 39 TGCT patients from the phase 1 extension study.

Mean exposure was about 65 weeks for ENLIVEN and 101 weeks for the phase 1 study. Long-term safety with similar to what we observed during the randomized period; that is, all patients had at least one adverse event and there were more grade 3

or 4 adverse events and serious adverse events in the pexidartinib group.

We observed a similar rate of AEs leading to discontinuation between the patients randomized to pexidartinib and those who crossed over to pexidartinib from placebo. Fifty-six percent of patients randomized to pexidartinib had an AE leading to interruption or reduction compared to 67 percent of patients in the crossover group.

When we look at the most frequent treatment-emergent adverse event across these three cohorts, the profile is quite consistent; again, the cutoff of January 2018. We see no new safety signal with longer exposure to pexidartinib. Hair color changes remains the most frequent adverse event along with fatigue, nausea, and AST/ALT increases.

I'd also like to briefly mention that we have performed a 90-day safety update with safety data for both phase 1 and ENLIVEN through August of 2018, and it is completely consistent with what we saw for the submission cutoff in January 2018.

With a 90-day safety update, there were no new late-emerging toxicity with continuation of treatment. There were no new cases of mixed or cholestatic hepatotoxicity in these three cohorts.

In summary, pexidartinib is associated with mostly low-grade and reversible adverse events. Adverse events occurring more frequently with pexidartinib compared to placebo included hair color changes and fatigue. Pexidartinib was generally well-tolerated, especially in the context of the extreme disease burden associated with TGCT in the indicated population.

I would now like to hand over this presentation to Dr. DeLeve, who will review the hepatic safety data for pexidartinib.

Applicant Presentation - Laurie DeLeve

DR. DeLEVE: Thank you, Yver.

Good morning. My name is Laurie DeLeve. I'm a professor of medicine at the University of Southern California, and I was a member of the hepatic events adjudication committee. I'm a paid consultant, but I have no financial interest in the

outcome of this meeting.

Now that you've seen the general safety profile for pexidartinib, I would like to walk you through the liver-specific safety data that we've identified among both TGCT and non-TGCT patient populations. I'd like to begin this section by highlighting that the hepatic adverse events of special interest can be divided into two clinically distinct presentations, both of which primarily occurred in the first 8 weeks.

The first type is characterized by aminotransferase elevations, which occur in the absence of significant alkaline phosphatase or bilirubin elevation, and are frequent, dose dependent, and generally low grade.

The second type is mixed or cholestatic hepatotoxicity, defined as alkaline phosphatase elevation twice the upper limit of normal and of liver origin, which may or may not be accompanied by aminotransferase elevation. The second type can be characterized as uncommon and idiosyncratic, and while they are rarely serious, they can be life

threatening.

First, let's look at the lab data for the isolated aminotransferase elevations. Here we see the number of patients in the randomized treatment group who had either AST or ALT elevations by severity. More than half of patients in the pexidartinib group had some elevation of AST or ALT but less than 3 times the upper limit of normal, and 27 percent of patients had elevations greater than or equal to 3 times the upper limit of normal.

At the bottom of the table, we see the lab data for the uncommon but mixed or cholestatic hepatotoxicity. You can see there were no true Hy's law cases as defined by ALT/AST greater than or equal to 3 times the upper limit of normal, with concomitant increases in total bilirubin greater than or equal to 2 times the upper limit of normal in the absence of alkaline phosphatase increase greater than 2 times the upper limit of normal.

There were 3 patients, or 5 percent, treated with pexidartinib who experienced mixed or cholestatic hepatotoxicity as defined by alkaline

phosphatase of liver origin greater than or equal to 2 times the upper limit of normal and proportionately higher elevations of alkaline phosphatase than aminotransferase elevations as defined by a mathematical formula.

Regarding the mechanism of the observed isolated aminotransferase elevations, it is worth noting that this has been seen with other CSF-1R inhibitors, including monoclonal antibodies, and it is likely that this is related to CSF-1R inhibition. Although this link has been demonstrated in the literature, it has not yet understood how CSF-1R inhibition causes hepatotoxicity. Importantly, the observed increase in aminotransferases were dose dependent and responded to dose interruptions or dose reductions.

Shown here is an example of a patient who had marked elevation of ALT with a daily dose of 800 milligrams of pexidartinib. ALT responded to dose interruption, and the patient was rechallenged with a reduced dose of 600 milligrams per day but at a second lower elevation of ALT. No recurrence

or aminotransferase elevation occurred after a further dose reduction to 400 milligrams per day. This is a clear demonstration of the dose dependence under reversibility of the hepatocellular hepatotoxicity associated with pexidartinib.

There were a total of 10 cases of mixed or cholestatic hepatotoxicity that occurred across the development program. None of these cases were considered probably related to pexidartinib the adjudication committee. In the TGCT population, there were 5 cases of mixed or cholestatic hepatotoxicity. Four cases resolved within 1 to 2 months and one ductopenia case took 7 months to resolve.

The details for all of these cases are available in the briefing document. I'd like to discuss the details of the 7-month ductopenia case. This is a case of a 75-year-old woman with TGCT, who developed ductopenia and cholestasis, lasting about 7 months. As background, ductopenia is defined as a reduction in the number of

intrahepatic bile ducts.

On day 1, the patient started pexidartinib at 1000 milligrams per day and was dose reduced to 800 milligrams per ENLIVEN protocol on day 15. On day 31, pexidartinib was permanently discontinued due to events of increased AST, alkaline phosphatase and bilirubin, as well as nausea and vomiting.

On day 72, her liver biopsy showed mild fatty liver with ductopenia, indicating damage to bile ducts. There was no significant inflammation or fibrosis. After 7 months, her bilirubin trended downward and eventually normalized. The events of liver disorder, bilirubin increase, and aspartate aminotransferase increase were considered related to pexidartinib.

Here we have a summary table showing the 5 cases of mixed or cholestatic hepatotoxicity in the non-TGCT population, including 2 cases for investigator-initiated studies. Four of these cases were adjudicated as probably related to pexidartinib and one had insufficient data. All of

these cases are available for review in the briefing document.

In the interest of time, I would like to review 2 cases that were prolonged and significant. The first case involved a 60-year-old female with breast cancer who was taking concomitant paclitaxel. On day 18, pexidartinib was discontinued because of cholestatic hepatotoxicity consistent for the managing [indiscernible] bile duct syndrome. This case resulted in a liver transplant at 20 months, after which the patient recovered.

The other case involved a 66-year-old female with progressive vaginal melanoma. She was assessed as having cholestasis with hyperbilirubinemia. She died in the context of melanoma hyperbilirubinemia. She died in the context of melanoma hyperbilirubinemia and cachexia 3 months after discontinuing treatment with pexidartinib, and there were insufficient data for adjudication. As with many other drugs that cause cholestasis, the mechanism of pexidartinib-induced

cholestasis is not well known.

With respect to hepatic adverse reactions, pexidartinib is associated with frequent, dose dependent, and manageable aminotransferase elevations that are associated with the pharmacological effect of CSF-1R inhibition. Pexidartinib is also associated with a low incidence of idiosyncratic mixed or cholestatic hepatotoxicity that is rarely severe but can be prolonged or irreversible, and has an observed onset within the first 2 months of treatment. This reaction was identified in 10 out of 798 subjects, which is 1.3 percent of patients across the development program.

Daiichi Sankyo conducted a number of investigations to better understand the mechanism and risk factors for pexidartinib-associated cholestatic hepatotoxicity. However, no risk factors have been identified and the mechanism remains unknown.

Although we cannot completely eliminate this potentially life-threatening risk of severe mixed

or cholestatic events, the goal is to reduce the risk of hepatotoxicity through careful monitoring of liver function and early intervention with drug discontinuation and other measures for the proposed label of REMS. In addition, the proposed patient registry will help us better understand the hepatic safety profile over time.

Now, I would like to invite Mr. Richards to the podium to discuss our proposed REMS in more detail. Thank you very much.

Applicant Presentation - Eric Richards

MR. RICHARDS: Now that we have presented the efficacy and safety profile of pexidartinib, I would like to walk you through the proposed risk evaluation and mitigation strategy, which is intended to support the appropriate use of pexidartinib.

The details of the REMS are under review by the FDA, and undoubtedly there will be some changes, but I will provide you with a high-level overview right now. Daiichi Sankyo is committed to working with the agency to establish an effective

REMS.

The REMS was proposed by Daiichi Sankyo as part of the NDA submission. It is designed to mitigate and further characterize the risk of serious and potentially fatal hepatotoxicity. Pexidartinib will be available only to stakeholders who have been trained and certified. In addition, based on recent discussions with FDA, a patient registry has been added to the REMS to further characterize the hepatotoxicity profile of pexidartinib, especially in the long term.

To become certified to prescribe pexidartinib, prescribers must review the prescribing information and REMS training materials, and then pass a knowledge assessment. They are responsible for completing patient enrollment, status, and adverse event forms for each patient, and counseling patients using the patient guide.

The prescriber must also conduct liver blood tests at baseline and frequently during treatment, particularly within the first several months. The

labeling will include clear instructions to prescribers regarding when to withhold or permanently discontinue treatment with pexidartinib based on the results of liver tests. The specific instructions are being actively discussed with the FDA.

Patients must review the patient guide which describes the risk of treatment, liver, blood test requirements, and the clinical signs and symptoms of hepatotoxicity. Patients must enroll in the REMS and registry by completing the patient enrollment form with their prescriber. Key risk mitigation measures include compliance with liver blood tests and immediately stopping pexidartinib and reporting signs or symptoms of potential hepatotoxicity to their doctor.

Pexidartinib will be distributed only through specialty pharmacies, and both wholesalers and pharmacies must complete a certification process to dispense pexidartinib. Pharmacies will be required to verify that the prescriber is certified prior to dispensing each prescription.

They must also ensure that the patient is enrolled in the registry and authorized to receive the drug. For the first 3 months of therapy, only a 30-day supply of pexidartinib is permitted to be dispensed.

As I mentioned, patients must also be enrolled in the registry before they can receive pexidartinib. The goal of the registry will be to further characterize the risk of hepatotoxicity, especially with long-term treatment and inform risk risk mitigation strategies. The registry will collect demographic and baseline hepatic information.

Patient status updates will be required periodically during treatment, and these updates will collect information regarding patient treatment status and note any laboratory abnormalities and related procedures. The occurrence of a laboratory abnormality will also trigger an adverse event form, which will collect additional detailed information.

In summary, the goal of the REMS, which

includes an educational component and limited distribution, is to mitigate the risk of hepatotoxicity. The patient registry will facilitate greater understanding of the risk and inform future risk mitigation strategies. We look forward to your feedback today and to further dialogue with the agency on how to best use these tools to protect patients' safety.

I will now hand the presentation over to Dr. Tap to provide his clinical perspective on the use of pexidartinib in patients with TGCT.

Applicant Presentation - William Tap

DR. TAP: Thank you, Mr. Richards.

I will round out the presentation today with some thoughts on what this drug means to clinicians and patients alike. As we've described, TGCT represents a spectrum ranging from a surgically curable tumor to a highly recalcitrant disease that changes the trajectory of otherwise young and healthy patients' lives.

For this latter group of patients, the benefit of pexidartinib was clearly evident in the

ENLIVEN study, even in cases with long-standing disease associated with extensive joint destruction and clinical morbidity. However, we acknowledge that the use of pexidartinib is not without risk, but for those patients with recalcitrant disease, we have to weigh the risk and benefit of pexidartinib against further non-curative, highly morbid surgery. These are the types of discussions that we routinely have with our patients in the clinic.

Take this young nurse, for example, with a large tumor of the right knee. She had been living with her disease for several years. She was unable to straighten her knee, required a cane, was taking narcotics, and was unable work. Her options were limited to morbid surgeries every few years, and she was seriously considering an above the knee amputation.

She chose to be treated with pexidartinib and had a dramatic response. After 4 months, her knee swelling and range of motion improved. She no longer required narcotics. She could walk

unassisted, and importantly, she went back to work. She has remained on therapy and continues to do well.

Here's another example of a patient with a tumor of the ankle who improved dramatically despite not having an objective RECIST response. At baseline, his mobility was greatly impacted and he was planning to quit work. After 18 months of treatment, his ankle was correctly aligned, and he has returned to his hobbies such as playing golf and tennis.

Finally, this patient was diagnosed in 1988 and had no other option but surgery. Over nearly 25 years, she had more than 20 surgeries and required regular red blood cell transfusions due to the inflammatory nature of this disease. This patient presented to medical oncology with horrible disfigurement and functional impairment.

Again, the patient had a profound response to pexidartinib on the ENLIVEN study with limited toxicity, and she remains on treatment today after 2 and a half years with continued regression of her

tumor. Her worst pain score went from 5.6 at baseline to 0.6 at week 25.

These are the patients facing the dilemma that the proposed indication addresses and for whom the benefit of pexidartinib outweighs the risks. For the medical community, having pexidartinib allows for a personalized, multidisciplinary approach to care for a previously neglected disease. For the patient, pexidartinib can transform their journey and take us beyond morbid surgeries. As ENLIVEN showed us, pexidartinib allows these patients to return to work, resume their hobbies, and move on with their lives.

Thank you. This concludes the sponsor presentation. We are looking forward to your questions.

DR. RINI: Thank you. We'll now proceed with presentations from FDA.

FDA Presentation - Christy Osgood

DR. OSGOOD: Good morning. My name is Dr. Christy Osgood, and I am the clinical reviewer

for the new drug application 211810, pexidartinib, submitted by Daiichi Sankyo, referred to as the applicant for the remainder of this presentation. I, along with my colleague, Dr. Mallorie Fiero, the statistical reviewer of this application, will be giving the FDA presentation for today's ODAC.

This is the multidisciplinary FDA review team for the pexidartinib application. The main issues with the new drug application include the assessment of clinical benefit and characterization of liver injury caused by pexidartinib.

The assessment of benefit of pexidartinib in patients with tenosynovial giant cell tumor, or TGCT, is based on a statistically significant improvement in overall response rate when pexidartinib is compared to placebo.

In a slow-growing disease that is progressive and debilitating, the result of overall response rate generally requires supportive efficacy data. Clinical outcome assessments were planned to provide evidence of alleviation of the symptomatic aspects of TGCT. The analysis of some

of the clinical outcome assessment secondary endpoints demonstrated a statistically significant improvement in mean change from baseline to week 25.

The interpretability of these results is limited due to several factors, including uncertainty regarding the threshold for what constitutes a clinically meaningful within patient change in range of motion and a high level of missing data at week 25.

For the second issue, pexidartinib causes liver injury. The majority of patients who receive pexidartinib will experience elevations in transaminase values; 2 to 5 percent of patients experience more severe liver injury. Additionally, 2 of the 768 patients treated with pexidartinib experienced irreversible hepatotoxicity. One patient died and the other required a liver transplant.

Liver biopsies show a pattern of bile duct injury evidenced by ductopenia and cholestasis. This raises concern that the liver injury may be

progressive, subacute, or chronic, and potentially lead to clinically important sequelae. Additionally, across the development program, a small number of patients have been treated for more than one to two years. Therefore, there is a lack of understanding of the potential long-term effects of pexidartinib.

This is the outline of our presentation. We will begin with a background followed by the efficacy and safety results in issues. We will conclude with our questions for the advisory committee. We will begin with the background for the application.

As the applicant has already presented, this slide shows the proposed indication and dosing regimen. TGCT is a rare non-malignant tumor affecting the synovium and tendon sheaths. Although it is not a malignant disease, it does cause significant progressive and debilitating symptoms, including pain, stiffness, and functional impairment. Surgery is the primary treatment. In patients with unresectable disease, there are no

approved systemic therapies.

FDA agrees with the regulatory history as presented by the applicant. FDA would like to provide additional details about the events important to our discussion today. As noted by the red boxes, the pexidartinib clinical development program was placed on partial hold on two separate occasions for severe events of hyperbilirubinemia and liver injury.

As a result of these two clinical holds, additional risk mitigation strategies were incorporated in the protocol and the development program as outlined in the purple box.

Additionally, as outlined in the orange boxes, the applicant proposed to revise the ordering of secondary endpoints due to a large amount of missing data at week 25. A meeting was held at FDA after which the applicant decided to reorder the endpoints prior to any unblinding of the data.

Now, Dr. Fiero will present the efficacy results and issues with the application.

FDA Presentation - Mallorie Fiero

DR. FIERO: Thank you, Dr. Osgood.

My name is Mallorie Fiero, and I am the statistical reviewer for this application. First, I will describe the estimation of clinical benefit with efficacy results, some of which have already been presented by the applicant.

With that, I will detail our concerns of estimating the treatment effect of secondary efficacy endpoints due to substantial missing data, then I will interpret our assessment of clinical benefit of secondary endpoints, which entailed addressing several issues that limit the interpretability of the observed result, including issues of revising the hierarchical testing plan for secondary endpoints; after trial completion; and limited information regarding the clinical meaningfulness of the secondary endpoints.

There were two studies that provided evidence of clinical efficacy of pexidartinib on the TGCT population, the ENLIVEN trial and study PLX108-01. The trial designs and characteristics

summarized in this table were also presented by the applicant. The pivotal study of ENLIVEN was double blind with 61 patients randomized to pexidartinib and 59 patients randomized to placebo.

FDA concurs that ENLIVEN demonstrated a statistically significant difference in the primary efficacy endpoint of overall response rate, or ORR, between pexidartinib and placebo. At week 25, the ORR was 38 percent in the pexidartinib arm compared to no patients achieving a response in the placebo arm.

It is noteworthy that at the data cutoff date of March 27, 2017, the ORR was 39 percent in the pexidartinib arm as reported in the briefing document. The results presented in this slide reflect the correction and ORR at week 25 after the applicant's reassessment of scans based on the later data cutoff date of January 31, 2018.

Among the patients with a confirmed response in ENLIVEN, only one patient had progressive disease in follow up. Tumor response was durable among patients who were followed for 6 months or

longer. The supportive study PLX108-01 showed an ORR of 49 percent at week 25.

The primary efficacy analysis for ENLIVEN was prespecified at a landmark of 25 weeks. However, with longer follow-up, tumor response rates were as high as 52 percent for patients randomized in pexidartinib, 2 in ENLIVEN, and 62 percent for patients in study PLX108-01.

As previously described by my clinical colleagues, TGCT can be debilitating, but the tumor is slow growing. These characteristics pose a challenge in evaluating the durability of tumor responses in the ENLIVEN trial. Patients with TGCT experienced symptoms such as pain, stiffness, swelling, and impairment in range of motion, which can cause severe functional impairment. Therefore, the assessment of clinical benefit of pexidartinib can be supported by the alleviation of symptomatic aspects of TGCT.

The applicant proposed clinical outcome assessments as secondary endpoints to assess TGCT's specific symptoms and functional impacts. A

clinical outcome assessment, or COA, is a measure that describes how a patient feels, functions, or survives. A key issue for this application is whether the results of the COA endpoints provide evidence of benefit for the functional impacts of TGCT.

In this application, a substantial amount of missing data was observed for the secondary COA endpoints. The FDA guidance for industry on patient-reported outcome measures states that missing data are a potential source of bias and can compromise the advantages created by randomization.

As highlighted in the red box, the proportions of missing data for the 4 COA endpoints in ENLIVEN ranged from 27 to 43 percent. Reasons for missing data included discontinuation due to adverse event, patient noncompliance, and administrative issues.

The percent of missing data for physical function, worst stiffness, and brief pain inventory, worst pain response, or BPI 30, is much higher than what is acceptable for reliable

estimation of clinical benefit. Therefore, we focused on interpreting range of motion, which was reported by a blinded third party assessor but still had over a quarter missing data at the time of the primary analysis.

The ENLIVEN trial demonstrated a statistically significant improvement in mean change from baseline range of motion at week 25 for the pexidartinib arm compared to the placebo arm. The trajectories of mean change from baseline in range of motion by treatment arm are shown in the figure on the left. At week 25, there was an average of 15 percent within patient improvement in the pexidartinib arm compared to a 6 percent within patient improvement in the placebo arm.

The sample sizes below the trajectories show that there were 27 percent missing in the placebo arm and 26 percent missing in the pexidartinib at week 25. The waterfall plot of change from baseline at week 25 by treatment arm is shown in the figure on the right, where the red bars indicate pexidartinib patients and the blue bars

indicate placebo patients. All bars above the X-axis indicate an improvement in range of motion from baseline. The plot shows that the majority of patients in the pexidartinib arm improved in range of motion.

An exploratory analysis of range of motion by tumor response showed that improvement in range of motion was, on average, higher for responders compared to non-responders in the pexidartinib arm as shown in this figure. It is notable that the percent of missing range of motion assessments was less for patients who had a tumor response.

Though the analysis of range of motion was not precluded due to missing data, the proportion of patients with missing week 25 assessments is not minimal and can cause bias in the estimation of effect. One concern is that is that missing data may be informative, which means that missingness could be related to the range of motion score even after adjusting for observed data.

For example, patients with missing range of motion assessments may be missing because their

worsened range of motion affects the patient's willingness or ability to complete an assessment. Thus, the results of range of motion may lead to biased interpretation because only patients who were potentially well enough were assessed.

In the ENLIVEN trial, although the percent of missing range of motion data was similar across the two treatment arms, the reasons for missing data were different for each arm. Half of the patients in the pexidartinib arm were missing due to adverse event, while patients in the placebo arm were mostly missing due to reasons such as withdrawal by patient or investigator decision. The differential reasons for missing data across arms could indicate informative missingness.

The FDA and the applicant performed multiple post hoc sensitivity analyses to address the concern of informative missingness for range of motion. In other words, we evaluated how much results change if we assumed patients with missing range of motion assessments were worse than what was assumed in the prespecified analysis.

The applicant presented a sensitivity analysis that included only patients with baseline and post-baseline assessments. However, this sensitivity analysis did not address the concern of informative missingness.

Another type of sensitivity analysis is a tipping-point analysis. This is a conservative approach in which data are imputed to identify a tipping point that will reverse the study's conclusion. Thus, the purpose of this tipping-point analysis is to determine the percent range of motion worsening needed in the pexidartinib arm to reverse significance with a p-value greater than 0.05.

A simplified plot demonstrating the tipping-point analysis is shown in the figure on the right. The solid black line shows the trajectory of mean change from baseline at week 25 for the 45 patients with observed range of motion data. The dotted lines show the trajectories of the assumed mean change from baseline for the 16 patients with missing range of motion data.

More specifically, the prespecified analysis model assumes the patients with missing data have a slightly worsened range of motion improvement from baseline compared to the observed patients as indicated by the blue dotted line.

The tipping-point analysis assumes that patients with missing data have an even worsened range of motion improvement from baseline by 12 percent as indicated by the red dotted line. This was the point in which the overall effect of pexidartinib on range of motion was not statistically different from placebo.

Overall, the analyses show that there appears to be a treatment benefit of pexidartinib on range of motion, but due to missing data, the magnitude is unclear. Based on the prespecified and sensitivity analyses, the estimated within patient range of motion improvement in the pexidartinib arm ranged from 7 to 19 percent.

Next, I will discuss FDA's evaluation of the interpretation of the observed results for range of motion, which was limited by several factors.

First, I will discuss the change in the hierarchical order of secondary endpoints made by the applicant. Next, we evaluate potential unblinding of clinical assessors due to changes in hair color while on pexidartinib. Finally, we assess what constitutes a meaningful change in range of motion from the patient perspective.

Prior to unblinding the data, the applicant discovered a substantial amount of missing week 25 COA assessments specifically for the patient-reported endpoints of physical function, worst stiffness, and brief pain inventory worst pain response, or BPI 30. The applicant subsequently revised the hierarchical testing order of the secondary endpoints in the final version of the statistical analysis plan.

The applicant moved BPI 30 from the first to the last position, and range of motion was moved from the third to the first position in the hierarchy of secondary endpoints due to the higher completion rate. In general, changing the statistical analysis plan after trial completion is

strongly discouraged due to introduction of potential bias. However, FDA acknowledged the concern regarding the statistical validity of the originally proposed hierarchical analysis given the substantial amount of missing data.

Ultimately, it was the applicant's decision to change the hierarchy of secondary endpoints and is acknowledged as a weakness of the ENLIVEN results. It is noteworthy that the change in the hierarchy of testing did affect the statistical conduct of the study. Since BPI 30 was not statistically significant and was originally the first secondary endpoint to be tested, range of motion would not have been tested for inference.

Although range of motion was evaluated by a blinded third-party assessor, there was potential for unblinding because hair color change to white for 67 percent of the patients on pexidartinib. Since ENLIVEN is a double-blind study, this can cause unblinding of the clinical assessors, leading to potential bias and reporting of range of motion. Our exploratory subgroup analysis did not show any

differences in range of motion between patients whose hair color changed to white compared to those whose hair colored did not change.

Finally, we assessed what constitutes a meaningful change in range of motion from the patient perspective. Although there was a statistically significant difference between treatment arms for range of motion, this does not necessarily mean that patients experienced a clinically meaningful benefit. In general, FDA request that applicants propose and justify appropriate thresholds that would constitute as a clinically meaningful within patient change in the COA score of the target patient population.

Per the FDA guidance on patient-reported outcome measures, FDA encourages anchor-based methods to establish a threshold of clinical meaningfulness. An anchor-based approach would have evaluated the relationship between range of motion and another independent measure, such as another COA, to determine a clinically meaningful change. However, due to the substantial amount of

missing data and all other COA endpoints and global scales, this approach was not feasible.

The applicant proposed a positive 6.7 percent threshold for what constitutes a clinically meaningful within patient change for range of motion at the knee. The normal range of motion for the knee is 150 degrees, so a 6.7 percent improvement corresponds to a 10-degree improvement for the knee.

The applicant stated that a threshold was proposed for the knee only because there is no widely used standard of improvement in range of motion for other joints, as it depends on the specific joint as well as the degree of impairment at baseline. Additionally, the applicant's justification for this threshold at the knee was based on input from a single expert and review of literature, which is also very limited.

It is noteworthy that there may be a range of thresholds that could be interpreted from available literature. However, which thresholds would be meaningful have not been established.

The waterfall plot shown here presents the change from baseline range of motion score at week 25 for patients whose tumor location was at the knee. The red bars indicate the pexidartinib patients who had a tumor response, the purple bars indicate the pexidartinib patients who had no tumor response, and the blue bars indicate placebo patients who had no tumor response.

All bars above the X-axis indicate an improvement in range of motion from baseline. Note that 26 percent of patients had a missing assessment at week 25.

The dashed line shows that the 6 percent threshold that the applicant proposed is what constitutes a clinically meaningful within patient change. Forty-one percent of the patients in the pexidartinib arm and 18 percent of the patients in the placebo arm had a clinically meaningful improvement in range of motion in the knee, assuming a 6.7 percent threshold is acceptable. However, due to limited justification, it remains unclear whether a 6.7 percent improvement

represents a clinical benefit to patients whose tumor location is at the knee.

In summary, we concur with the applicant that the trial demonstrated a statistically significant improvement in ORR and range of motion for pexidartinib compared to placebo. Although a treatment benefit was demonstrated for range of motion, the interpretation of the effect is unclear due to missing data and limited information on clinical meaningfulness for the target patient population in ENLIVEN. The magnitude of improvement from baseline for patients on the pexidartinib arm was estimated to range from 7 to 19 percent with a lower estimate for the knee being as low as 6 percent.

Next, Dr. Osgood will continue the presentation with the safety evaluation.

FDA Presentation - Christy Osgood

DR. OSGOOD: Thank you, Dr. Fiero.

FDA based the primary evaluation for the safety of pexidartinib in the TGCT population on the ENLIVEN trial. The overall safety evaluation

of pexidartinib is presented for the first 25 weeks of treatment in order to allow for a comparison between the 61 patients randomized to pexidartinib and the 59 patients randomized to placebo.

This evaluation of safety included an analysis of adverse events, laboratory assessments, patient narratives, case report forms, and liver biopsy reports when available. Additionally, in order to better understand the liver injury in the indicated population, FDA performed a detailed evaluation of laboratory assessments, adverse events, and patient narratives for the entire TGCT population that received pexidartinib, which included 130 patients.

This slide presents an overview of the safety from the first 25 weeks of ENLIVEN. Almost all the patients in each arm experienced an adverse event. Notably, a higher proportion of the patients randomized to pexidartinib experienced a grade 3 or 4 adverse event, a serious adverse event, or an adverse event leading to discontinuation, dose reduction, or dose

interruption when compared to patients randomized to placebo.

Adverse events reported in more than 20 percent of patients in the pexidartinib arm are displayed in this table. Most relevant to our discussion today, 39 percent of patients experienced an increased AST and 28 percent of patients experienced an increase in ALT as reported by the investigator.

Due to the fact that adverse events are only recorded when an investigator report to them, adverse event analysis may not capture all cases of liver injury that occur in a development program. Analysis of the clinical laboratory values may provide a more complete picture of patients with TGCT who experience liver injury throughout the pexidartinib development program.

The third column of this table, highlighted by the red box, displays the proportion of patients randomized to pexidartinib in part 1 of ENLIVEN that had elevated transaminases and/or bilirubin. The majority of patients treated with pexidartinib

experienced elevated ALT and AST, and a third of patients experienced an AST or ALT value at least 3 times the upper limit of normal.

Twelve percent of patients experienced elevated total bilirubin when compared to baseline. As seen in the last column, evaluations of AST, ALT, and bilirubin in the pooled TGCT population showed a similar pattern to the patients with pexidartinib in part 1 of ENLIVEN.

According to the FDA guidance on drug-induced liver injury, Hy's law can be used to identify cases of drugs causing hepatocellular injury sufficient to impair bilirubin excretion. To be a Hy's law case, all of the following criteria must be met: an AST or ALT greater than 3 times the upper limit of normal and a total bilirubin greater than 2 times the upper limit of normal without initial findings of cholestasis evidenced by increased alkaline phosphatase, and no other reason for the combination of increased transaminases and total bilirubin may identified.

For ENLIVEN, strict Hy's law criteria could

not be used to identify patients with severe liver injury because all the patients with an increase in ALT or AST and total bilirubin had a concomitant elevation in alkaline phosphatase. Given that bile duct injury has been observed with pexidartinib use, the presence of cholestasis represented by an increase in alkaline phosphatase may not represent a separate process.

Therefore, we used the criteria of a total bilirubin greater than equal to 2 times the upper limit of normal and an AST or ALT greater than or equal to 3 times the upper limit of normal, regardless of alkaline phosphatase elevation to identify patients with severe liver injury.

Using this definition, 4.9 percent of patients in part 1 of ENLIVEN and 3.1 percent of the pooled TGCT population treated with pexidartinib experienced lab abnormalities associated with severe liver injury, as highlighted by the red box in the table.

The majority of the AST and ALT elevations that incurred in part 1 of ENLIVEN occurred during

the first 2 months of therapy with pexidartinib. This figure shows an analysis of the timing of transaminase elevations based on laboratory data. On the X-axis are the weeks relative to when the patients started therapy, and on the Y-axis is the result of an AST or ALT lab compared to the upper limit of normal.

The gray line denotes the upper limit of normal. The initial elevations in most patients occurred prior to week 9, and the remaining elevated values represent patients who reoccurred with rechallenge or patients as they recovered from their liver injury. A similar pattern was seen with the elevations in bilirubin experienced by patients treated with pexidartinib in part 1 of ENLIVEN.

In order to address the increases in transaminase and bilirubin observed in ENLIVEN, management guidelines for cholestatic hepatotoxicity were provided in the study protocol. In response to the two partial clinical holds, laboratory monitoring was increased and dose

modification and discontinuations occurred at lower AST, ALT, and bilirubin values.

The table on this slide displays the dose modification guidelines from the latest version of the protocol and show that for an AST or ALT elevation greater than 3 times the upper limit of normal, pexidartinib should be interrupted and only restarted once AST or ALT improved. And if the ALT or AST increase occurs concomitantly with an increase in bilirubin, pexidartinib should be permanently discontinued.

Fifty-five of the 61 patients in part 1 of ENLIVEN experienced elevated liver transaminases and/or bilirubin. Based on the dose modification guidelines provided in the protocol and keeping in mind that the dose modification guidelines changed over time, 40 of the patients required no intervention. Eight patients required dose interruption.

Of the 8 patients who required dose interruption, 4 successfully resumed pexidartinib either at the same or a reduced dose and were able

to stay on pexidartinib for the long term, and 4 had recurrence of transaminase elevations following rechallenge, ultimately leading to permanent discontinuation of pexidartinib; 4 patients had permanent discontinuation of pexidartinib without rechallenge, and 3 patients exclusively had dose reduction without an interruption.

All of the 55 patients in part 1 of ENLIVEN who experienced elevated transaminases and/or bilirubin improved. Although the majority of patients had laboratory values that returned to within normal limits or their baseline, 18 patients did not recover to within normal limits. Fifteen of these patients improved to 1.1 to 2 times the upper limit of normal, and 3 of these patients improved to 2 to 2.7 times the upper limit of normal.

This slide provides additional details about the outcome of the 3 patients in part 1 of ENLIVEN who experienced lab abnormalities consistent with severe liver injury defined by a total bilirubin greater than or equal to 2 times the upper limit of

normal and an AST or ALT greater than equal to 3 times the upper limit of normal. All of these patients had pexidartinib permanently discontinued at the first occurrence of liver injury.

Despite discontinuation of pexidartinib, these patients had laboratory abnormalities that continued to increase. Most notably, total bilirubin continued to increase to peaks ranging from 7 times the upper limit of normal to 15 times the upper limit of normal. Additionally, there direct bilirubin values ranged from 4 times the upper limit of normal to 84 times the upper limit of normal.

Finally, patients had prolonged recovery times ranging from 2 to 7 months, and 2 of the patients required treatment beyond discontinuation of pexidartinib, including hospitalization, in order to recover from their significant liver injury.

In order to provide a more complete analysis of the liver injury caused by pexidartinib, the applicant provided a broader safety database that

included 768 patients; 630 from commercially sponsored trials and an additional 138 patients from investigator-initiated trials. In the broader database of patients enrolled in commercially-sponsored trials, the incidence of patients who experienced labs consistent with severe liver injury was 2.5 percent.

Given this information and a review of the cases of severe liver injury, this broader patient population did not change the overall conclusion about hepatotoxicity. However, the broader safety database provided 2 cases of irreversible liver injury.

This slide provides a summary of the relevant clinical course for the two cases of irreversible liver injury. The first patient had early-stage breast cancer and was enrolled in an investigator-initiated trial. She received pexidartinib in combination with paclitaxel as adjuvant therapy and experienced transaminase and bilirubin elevations.

During her initial workup for elevated

transaminases and bilirubin, it was discovered that she had cholecystitis and was treated with a cholecystectomy and antibiotic therapy. Despite optimal treatment for her cholecystitis and permanent discontinuation of pexidartinib and paclitaxel, she progressed to liver failure and received a liver transplant 20 months after initiating pexidartinib.

The second patient had metastatic melanoma with metastatic disease in the liver, and was treated with the chemotherapeutic agent seen here. Upon the first occurrence of liver injury, the patient had all treatments for melanoma discontinued. The patient's liver injury was treated with up to 20 unspecified herbal remedies as liver-protecting therapy.

Additionally, she received bilirubin absorption therapy and other unspecified liver-protecting therapy. She eventually refused further medical treatment as well as food and water. Her liver failure progressed, and she died 4 months after initiating pexidartinib therapy.

The overall safety database also provided biopsy results for 8 of the 768 patients who were treated with pexidartinib as a single agent or in combination with chemotherapy or targeted agents. One of these biopsies was obtained in a patient enrolled in ENLIVEN, while the other 7 were obtained in patients with other solid tumors.

Seven of these biopsies showed ductopenia, cholestasis, or bile duct injury. The eighth patient had a biopsy that revealed mild apoptotic hepatocellular injury with minimal inflammation and no fibrosis. No patients had a second biopsy to evaluate for progression or resolution of their biopsy findings after hepatic laboratory values normalized.

Given the data provided by the applicant, FDA has concluded that pexidartinib causes liver injury. Across the development program, 0.3 percent of patients experienced irreversible liver injury. Although none of the cases of irreversible liver injury occurred in a patient with TGCT, 3.1 percent of patients with TGCT and 4.9 percent

of patients in part 1 of ENLIVEN who received pexidartinib had laboratory values consistent with severe liver injury.

In ENLIVEN, the majority of patients who receive pexidartinib experienced elevations in liver transaminases and 12 percent of patients experienced an increase in bilirubin. Although all of the patients in ENLIVEN improved with no intervention, dose reduction, dose interruption, and/or discontinuation, there were two cases that had a prolonged time to recovery, requiring more intervention.

Although the ENLIVEN trial and the broader safety database has identified liver injury related to treatment with pexidartinib, there remain uncertainties. The mechanism of action causing bile duct injury is unknown. Liver biopsies were obtained in only 8 of the 768 patients in the pexidartinib safety database, and therefore, it is uncertain how many patients with elevated transaminases and bilirubin experienced bile duct injury upon exposure to pexidartinib

The biopsies that were obtained reveal a pattern of injury to bile ducts and ductopenia. Because serial biopsies were not performed in any patients, it is unknown whether the injury to bile ducts is progressive and whether it occurs even in the setting of an improvement or normalization of biochemical laboratory parameters.

Furthermore, it is unclear whether pexidartinib causes subacute and/or chronic or indolent injury that may result in cirrhosis and liver failure, leading to the need for a liver transplant or causing death. Therefore, it is unclear whether measures taken to achieve normalization of transaminase addresses any subclinical effects of the drug on the liver.

An additional area of uncertainty is the potential long-term effects of pexidartinib. In the TGCT population, pexidartinib will be indicated for long-term use, and the effects of long-term exposure have not been defined. Only 69 patients have been treated for more than 18 months, and only 8 patients have been treated for more than 4 years.

This limited experience does not provide comprehensive data to evaluate what will happen with long-term exposure to pexidartinib.

To help mitigate the risk of liver injury due to pexidartinib, the applicant is proposing a risk evaluation and mitigation strategy, or REMS. The FDA can require sponsors to develop and comply with REMS programs, if determined necessary, to ensure the benefits of a drug outweigh its risks. A REMS with elements to assure safe use, or ETASU, can be required for a drug if FDA determines that the product is effective but is associated with a serious risk and can be approved only if such a strategy is in place to ensure the benefits outweigh the risks.

Given the risks that have been discussed in this presentation, FDA feels that a REMS is necessary to try and prevent the risk or reduce the severity of the risk, and to collect more information about the risk of hepatotoxicity associated with long-term use.

The proposed REMS consists of a

communication plan and elements to assure safe use. The communication plan will inform likely prescribers about the indicated population and the serious risk of liver injury. The elements to ensure safe use include prescriber education and certification to ensure that prescribers are educated on the risks, the need for frequent laboratory monitoring, and to counsel patients.

Each patient will be required to enroll in a patient registry to assess postmarketing safe use and collect more information to further characterize the risks of hepatotoxicity. Additionally, there will be a pharmacy certification to ensure that each prescriber is educated, that the patient is enrolled in the registry prior to dispensing, and that pharmacies only dispense a 30-day supply of the drug.

The purpose of the patient registry is to assess postmarketing safe use and further characterize the acute chronic and irreversible hepatotoxicity. The registry will enable collection of baseline information, including

laboratory values and concomitant medications.

The registry will require periodic status reports on each patient. The status reports will include information on each patient and any events they may experience, including information about diagnostic workup in patients who experience acute long-term or irreversible liver toxicity.

In conclusion, patients with symptomatic TGCT, which is associated with severe morbidity or functional limitations and which is not amenable to improvement with surgery, have no available therapies.

Pexidartinib has demonstrated a statistically significant improvement in ORR and range of motion. However, there are limitations in interpreting the results for range of motion due to missing data and insufficient evidence for a clinically meaningful threshold for improvement.

Additionally, it is known that pexidartinib causes liver injury that may be severe or irreversible. This liver injury has not been completely characterized or defined for the

population that will receive pexidartinib for long-term use if pexidartinib is approved for the treatment of patients with symptomatic TGCT.

FDA will now present the discussion topics and questions for the ODAC. FDA's discussion topic is discussed whether the benefits of pexidartinib, as characterized by a clinically meaningful reduction in tumor burden and an improvement in range of motion, outweigh the risk of hepatotoxicity.

The voting question is, does the demonstrated benefit of pexidartinib outweigh the risks of the drug in the proposed indication? Thank you.

Clarifying Questions

DR. RINI: Thank you.

We'll now take clarifying questions for any of the presenters. Please remember to state your name for the record before you speak, and you can direct your questions to a specific presenter. If you just give Jennifer or myself a wave, if you have a question, we will write down a list and get

to all of you.

I'll go ahead and start. If the applicant could pull up slide CE-11? This side at the bottom shows predicted probability of complete resection. I have a question maybe for the orthopedic surgeon, and this relates to your indication wording, the last part of which is not amenable to improvement with surgery.

I guess the question is, if this drug is approved and gets out into the community, how translatable is that adjudication committee to a community setting, where an average orthopedic may have limited experience, or how do you actually predict that?

MR. RICHARDS: I'll invite Dr. Bernthal to address this question.

DR. BERNTHAL: Nick Bernthal, UCLA. The spectrum of disease that we see in TGCT is quite broad, and, admittedly, most of the orthopedic surgeons in the community are going to see localized disease, and that's the bulk of what we see.

If you don't mind bringing up the shoulder film, please?

As far as making a distinction between patients for whom this risk-benefit analysis makes sense, really. this is quite -- it's more dramatic and clear than I think we've been successful at showing. This is a patient who walked into my clinic earlier this month, and this is a patient who had a shoulder replacement, a proximal humerus placed 20 years ago, and has gone physician to physician with a non-functional arm for the last 20 years.

You can see that the tumor has eroded out all of the bone in the humerus. For those who aren't used to looking at films like this, there's also a soft tissue shadow of tumor going up over the clavicle and up into the neck. This is a patient for whom it's very clear that there is no surgical option. An amputation would not solve this patient's tumor burden because it's going up into the neck.

I think every patient with TGCT, with

diffuse type and recalcitrant TGCT, is going to have to have this decision made by a multidisciplinary team. My belief is that the dramatic majority of these patients are referred in to tertiary centers that have multidisciplinary tumor boards that are used to weighing risk-benefit of surgery versus medical therapies.

DR. RINI: Thank you.

Dr. Hoffman?

DR. HOFFMAN: A question I think also for Dr. Bernthal. In those patients with diffuse disease who have required a joint replacement, how common is it that there will be recurrence after the joint replacement? We've seen some serious examples, as you've shown us, but do the majority of patients still wind up with difficulty there?

MR. RICHARDS: Dr. Bernthal?

DR. BERNTHAL: Nick Bernthal, UCLA. It's varied, and it depends on the joint. The question of recurrence in TGCT is a complex one because oftentimes we have what is likely recurrent tumor that may or may not be symptomatic. So often

patients who get joint replacement may well have residual disease, but may have asymptomatic disease. And once you put the metal in for a joint replacement, getting MRIs and determining whether there is in fact disease present is very difficult radiographically.

To answer the question as clearly as I can, I would say that in the hip joint specifically, oftentimes arthroplasty procedures are more successful at alleviating symptoms for patients, but in the knee, we often get recurrent swelling and pain around the arthroplasty procedure.

DR. LEWIS: But, Dr. Bernthal, wouldn't you think that's the minority of patients? These were very dramatic pictures and, I mean, excellent presentations, but the recurrence in patients who have had joint replacements, it would be the minority of patients. So looking at this data in the presentations, this is a drug for the minority of the minority of patients.

I do have a question. In looking at the data, if it's a drug, really, for the minority of

minority patients, only less than 30 percent of the patients will respond to it.

DR. BERNTHAL: Nick Bernthal again, UCLA.

DR. LEWIS: That was Val Lewis, MD Anderson. I'm sorry.

DR. BERNTHAL: I agree a hundred percent that this is the minority of the minority. And as we talk about the epidemiology, this is the subset that's diffuse, the subset that is not cured by surgery, and the subset that's recalcitrant. So we're getting down the line to a very small number. I agree with that a hundred percent.

Was there a second part of the question?

DR. LEWIS: Just listening to that, even that subset, less than 50 percent will respond to the drug, will have a dramatic response. Reading through it last night and listening to the talk, it seems great for less than 50 percent of patients who get the drug.

DR. BERNTHAL: As far as the clinically meaningful impact on patients, if you can bring up the knee film. A lot of the data here clearly is

means, and with means, it's difficult to determine the issue and improvement a single patient is going to get. But I'd like to point out that when we look at range of motion, say, the FDA's data that was presented showed that the range, when you look at the statistics top and bottom within patient, is between 7 percent and 19 percent improvement.

If that's the mean, we're talking about the average patient's response between 7 and 19 percent within patient, remember that that's percentage points. I think one of the things that's gotten somewhat lost in the presentations and in the clarity is that that's based on a 150-degree normal knee. So you're multiplying every percentage by 1.5 to get what the range of motion improvement is.

So between 6 and 19 percent improvement is really a 10 to 25 degree average patient response to this, in the knee, which is the bulk of our patients. When you look on the top-right of that slide and you keep in mind what functional benefits matter to patients, these activities of daily living, between level walking and going up and

downstairs, that's a 15-degree difference. In and out of a chair is only a 10-degree difference.

So when we're talking about improving the average patient between 10 and 22-23 degrees, this is really, really a dramatic impact for the majority of patients.

DR. RINI: Thank you.

DR. LEWIS: Thank you.

DR. RINI: Dr. Weinfurt?

DR. WEINFURT: Kevin Weinfurt. I'm a little bit confused about the reasons for missingness the COA data. I guess I've heard and read a few different things, and I'm just trying to get a handle on this.

In the briefing document we were given from the sponsor, on page 58, the reasons are broken out with respect to discontinuation or other reason, and in the description of what goes into each of those, I noted that patient noncompliance was listed as being included under each of those.

So I was a little bit confused about where patient noncompliance went, and I think that

Dr. Fiero also referenced data, but we didn't see it, about a higher prevalence of AE related reasons for missing. This is kind of an important question about these missing data, and it would be great to get some clarification about the actual distribution of reasons by arm.

MR. RICHARDS: We'd be happy to do that. I'd like to invite Dr. Shuster to walk us through the different reasons for missing data.

DR. SHUSTER: Dale Shuster of Daiichi Sankyo. Allow me to put more detail on those reasons for missingness as you requested.

If we start with the patient disposition -- this was a slide presented by Dr. Tap -- as you noted, several patients came off early. This was before week 25. On the pexidartinib arm, there were 9, and 8 of those were due to an adverse event.

On the placebo arm, there were 11, and the majority of those were due to withdrawal of consent and an investigator decision. On the placebo arm, most of those came off after the DMC recommendation

and changed the study conduct. That gives the one group that we talk about, the patients who discontinued.

If we then look at the other reasons and look at them in more depth, this is looking at stiffness, one of the PROs. The other reasons are shown here over time. If you look at week 25, and the primary analysis time point is done, then you can see that the other reasons comprise 8 -- 18 pexidartinib and 12 on the placebo.

Now, if you look at what are more detail about those other reasons, you'll find that the first category, site scheduling of visit, is where most of these are. Site scheduling of visit, allow me to explain what this entails.

The patient-reported outcomes are entered on an electronic log pad. Those log pads are kept by the patients at home. For them to enter the patient-reported outcome for stiffness, which is reported each day for 7 days before clinic visit, the device needs to be programmed in such a way that it turns on at the next visit.

So if the sites do not schedule the clinic visit at the right time, or they don't schedule it at all, or often practically the schedule changes and they may need to reschedule the visit, then those would be cases when this entry of stiffness scores would not be.

The other issues are log pad. That's a technical issue. A device did not seem to be working properly or upload the data. Then the one you mentioned, patient noncompliance, is the number shown in that third column of the other.

DR. WEINFURT: If you could just tell us what's under all other reasons?

DR. SHUSTER: All other reasons comprises everything in the columns to the right of that.

DR. WEINFURT: Oh, I'm sorry.

DR. SHUSTER: It's just the total, and then we break them out. Of those 18, you can see pexidartinib, but they're 7, 3, and 8.

DR. FIERO: This is Mallorie Fiero with statistics. As you mentioned, Dr. Weinfurt, we noticed that the reasons for missing data were

different between the two treatment arms, although the percent of missing data was the same.

As you saw in the slide, although the slide was for more stiffness, we presented the table of missing reasons for range of motion, which was what we were most focused on in interpreting clinical benefit. Adverse event was one of the main reasons for the pexidartinib patients being missing, which is the reason why we performed sensitivity analyses for informative missing data. As we mentioned, we found a range of results from 7 to 19 percent within patient improvement.

DR. RINI: Thank you. Dr. Uldrick?

DR. ULDRICK: I wanted to follow up with two quick questions to better understand the totality of COA that was performed. First, I guess my question is to Dr. Fiero.

In looking at the plan, could you explain what a hierarchical assessment is and why you would not, as I understand it, look beyond the first test and rather look at the totality of the data, which are measuring different functional and

patient-reported outcomes that may be different?

DR. FIERO: That's a good question. For the hierarchical analysis, for a statistical analysis plan, we need to control for type 1 error. A hierarchical analysis is when you specify you test the primary endpoint first. And if that's found to be statistically significant, then we test in a specified order.

In the original statistical analysis plan, BPI 30, which was the brief pain inventory, was originally first secondary endpoint to be tested. But due to the substantial amount of missing data, the applicant came to FDA, prior to unblinding of the data, and proposed to reorder the hierarchy because of those missing data. They put BPI 30 from first to last, and then range of motion was put first.

So if the statistical analysis plan remained the same at the original protocol, or statistical analysis plan, range of motion would not have been tested. However, since the applicant did come to us, and they did this reordering prior to

unblinding, we acknowledge this as a weakness of the ENLIVEN results.

Does that answer your question?

DR. ULDRICK: Yes. It does answer my question. It still makes it hard to not look at the other data. I guess maybe a question is really to the sponsor to the rationale between the rank -- for the original ranking and the reordering of the ranking.

MR. RICHARDS: BPI and pain, as well as range of motion, were clinically relevant endpoints during the conduct of the study due to conduct change; for example, the DMC changes, along with the patient compliance, which can always be a difficulty when collecting patient-reported outcomes and these types of data.

It became apparent there was missing data. Range of motion was moved up because it was apparent that was going to be the least impacted by the missing data, and subjective, and clinically relevant, so we went ahead and moved it up.

We did discuss with the agency knowing it

was our decision. It was our decision to do this prior to unblinding, and in our discussions, the totality of the secondary endpoints would be part of the evaluation.

DR. ULDRICK: The second point related to that is whether or not that reaches the threshold for being clinically meaningful, and part of that depends on it being anchored to some other outcome. I was wondering if you could give an example of an outcome that one might look at for range of motion of the knee, if we're trying to interpret this.

DR. FIERO: First of all, I just wanted to clarify that we decided to focus on range of motion not necessarily because of the reordering, but it's because the substantial amount of missing data that we saw for physical function, and worst stiffness, and BPI 30, which was about 43 percent.

As you mentioned, we usually use an anchor-based approach, and the sponsor proposed a couple -- or they had a couple of anchor measures, which I believe they can expand on. But one example would be something like a physical

function. If you look at the relationship between the range of motion and physical function, the difference between physical function can help you determine what would be clinically meaningful for range
of motion. However, due to the substantial amount of missing data and the endpoints, we weren't able to perform that type of analyses.

DR. RINI: Dr Villalobos?

DR. VILLALOBOS: Yes. This is Vic Villalobos from the University of Colorado, Denver. This question's for Dr. -- I'm sorry. I'm forgetting his name -- the surgeon --

MR. RICHARDS: Dr. Bernthal and Dr. Tap.

DR. VILLALOBOS: I apologize. In your view of the data, were there a substantial number of patients that actually would have become resectable, based off of the responses that we were seeing?

MR. RICHARDS: Dr. Bernthal?

DR. BERNTHAL: Nick Bernthal, UCLA. That wasn't the intent of this study, and the data

wasn't followed that way. Honestly, I don't know. I can't answer that question. The intent of the study wasn't set up as a neoadjuvant trial. I just can't really speak much more to it.

DR. VILLALOBOS: And a question for Dr. Tap, then. In your experience with this drug in this trial, the real-world use of this data, considering the fact that very few of the patients in the placebo arm at 25 weeks had progression of disease, do patients require long-standing use of this drug to garner benefit?

MR. RICHARDS: Dr. Tap?

DR. TAP: William Tap, Memorial Sloan Kettering Cancer Center. This was actually a disease that, from a medical oncology standpoint and a clinical trial development standpoint, we knew very little about. One of the things that we had to do was really engage with the patient community to understand what they go through with this disease. And we're very thankful for that because they really taught us how disease in different joints can really affect what they go

through on a daily day-to-day basis.

What we can say is the results were dramatic, and the majority of patients had some improvement. We see that not only in shrinking within the tumor, but meaningful improvements to them. Most patients can discern their PVNS or TGCT pain from other aspects of pain, which you can understand having multiple surgical resections or a disrupted joint, there is that.

One of the most important questions that I think we need to answer as an academic community is how to best apply this drug moving forward. I think you raised two important questions. Could there be an adjunct for patients who have a tremendous response to treatment to say can we get them to surgery and properly clear the joint? But the other thing is what is the appropriate longitudinal use of this drug?

We were allowed to have dose reductions, dose modifications for patients, and it was very variable what we saw, even in patients who came off study. What had happened is a lot of times, we

would see stability of disease and symptoms. Sometimes we would see a slight increase in their patient-reported symptoms, what they would call, say, their TGCT pain or stiffness, but it is still unclear of how to use this drug longitudinally.

Now, most important for me is having the drug available so we can begin to answer these important questions with this community, and I think having that relationship between the patient and the clinician is going to be critical.

DR. VILLALOBOS: Now applying the risk-benefit ratio is a primary question here. For a situation where a drug has a small risk of causing significant toxicity and morbidity with hepatic failure and this implementation of this REMS program, would it not be more effective, actually, to have a dose-escalation approach rather than doing a high dose to begin with, with a higher risk, particularly within the first 8 weeks of actually developing these liver toxicities; having a lower dose escalation within the patient itself, particularly considering this has benign disease

where patients will not die from disease?

MR. RICHARDS: I can invite Dr. Tap's opinion, but we don't know. The mixed or cholestatic hepatotoxicity is idiosyncratic. Part of the intent behind the patient registry is to gather more information so that perhaps we can understand this a bit better. But I would invite Dr. Tap's opinion on this.

DR. TAP: Thank you. William Tap, Memorial Sloan Kettering. Again, a little piece of history, which I think is important with our lack of understanding of this disease. We felt it was very critical to have a placebo control. There is an inflammatory nature to this disease, so we didn't know if we could see spontaneous regression, say, as we see in desmoid tumors. A recent study in that disease showed about a 20 percent spontaneous response rate.

I think that was very important in how we design this study. The pharmacokinetics suggested -- and what we saw in the phase 1 studies, that there were rapid decreases within the

first few months of therapy with 1000-milligram per day dosing. When we had a 25-week period that we were looking for this initial analyses, potentially having quick remediation of symptoms and improvement was very important from a trial design standpoint and from a patient care standpoint.

I think your question, though, as what you're proposing is saying what is the practical approach to this, and do patients need that rapid decline in symptoms and maybe tumor response clinically? I think that's a very important question, and that would be something that, again, as the academic community, we would be very interested in asking; would we still see the same kinetics of response and how best to apply it?

But again, to me it comes down to actually having something systemically that we could do for these patients. The risk is critical of the hepatotoxicity, and that's what should weigh on all of our minds as clinicians. I think Dr. Bernthal mentioned that there's that initial multidisciplinary discussion to say, should medical

therapy be considered? If medical therapy is considered, really, the impetus then lies on the medical oncologist to understand the weight of the toxicities that you noted and what the disease is actually doing to the patient to have that appropriate risk-benefit discussion.

These are patients that come to our clinic, and we can spend some time before we immediately start a therapy. We can see what their symptoms are. We can enact other measurements. Some of the placebo patients actually did better when they went on to trial, and I attribute that to the multidisciplinary care they got when they came into a tertiary care center: pain, palliative care, adjustments of medications, physical therapy.

So there is some time to make these decisions, too, but in patients who really need the medication, then I think also that risk-benefit discussion would be really important.

DR. RINI: Thank you. Dr. Strader?

DR. STRADER: Doris Strader, University of Vermont. I have a question about the

hepatotoxicity. I struggle trying to decide risk-benefit in patients with a benign tumor in whom we do see changes in tumor size and volume. And as a result, probably that's what's related to the change in range of motion because the tumor's a little bit smaller, and trying to figure out who these people are.

If this were a life-threatening condition, it's easy. You'd say, okay, well you have to do something. This is not a life-threatening condition, so the question is, is the change in the size of the tumor and the change in range of motion, that may or may not be clinically meaningful to the patient, worth the risk of hepatotoxicity?

So my first question is I couldn't find anywhere, in any of the data that you mentioned, what the baseline AST and ALT were and what you consider normal ALT and AST. Everything says above the upper limit of normal, but that depends on what you consider normal.

Where I live in Burlington, Vermont, normal

is considered 40, and normal and healthy are two entirely different things. The AASLD has decided that healthy AST and ALT are 19 for women and probably 22-23 for men. But many places consider 40 normal. If you go further south, 70 is normal.

So the question is what was the normal value that started many patients that had side effects or older patients? I don't know if they were older patients with diabetes and heart disease and risk for let's say the metabolic syndrome who may have had a normal ALT of 39, which is not necessarily normal in the grand scheme of things. So I want to know if there's any indication as to what the normal value was on the majority of those patients.

MR. RICHARDS: Absolutely. I'd like to invite Dr. DeLeve to speak to this point. We have had some discussions in terms of BPI and labeling for those patients with baseline abnormalities. We don't have substantial evidence to say, no, you can't be a candidate for this therapy, but I would ask Dr. DeLeve for her opinion.

DR. DeLEVE: Laurie DeLeve, University of

Southern California. The blood was sent to a central, and I believe the upper limit of normal was 40.

Your second question was basically did we see NAPLD, and, yes, we had multiple NAPLD patients in the patients who were either diabetic or hyperlipidemic with hypertension, who had a different liver test pattern, the more fluctuating AST/ALT, alk phos. Those were adjudicated by the hepatic events adjudication committee as not related.

DR. STRADER: So that makes it a slightly more difficult situation because now you have patients who don't have a normal ALT to start, and some of them have another condition that may predispose them to the unclear hepatotoxicity of pexidartinib.

DR. DeLEVE: So they were not started on the study if their baseline was up --

DR. STRADER: Above 40 --

DR. DeLEVE: -- at the time of --

DR. STRADER: Above 40?

DR. DeLEVE: Correct. I think it was 40. ALT was 40.

DR. STRADER: Okay.

DR. RINI: Ms. Preusse?

MS. PREUSSE: A quick question. Courtney Preusse, consumer rep. Dr. Tap answered my first question. The second was just on slide CE-5, he mentioned that stratification of the ENLIVEN trial was stratified by upper versus lower extremity. And I'm wondering if there was any data to show that there was a benefit in one group versus the other.

I guess the underlying assumption would be if you rolled out the use of this drug in a more limited population, whether you would limit the number of severe adverse events.

MR. RICHARDS: To answer your first question of whether we saw a difference in the clinical activity of the upper versus lower extremity, on all the subgroups, the effect in terms of ORR and TVS was very, very similar across all the subgroups. The intent of the indication is to do

exactly that, is to limit it to only that population that really have no viable options because they're no longer amenable to surgery, and in these patients that were highly likely not to have a successful surgery, we saw similar effects across all of the subgroups.

DR. RINI: Dr. Halabi?

DR. HALABI: Thank you. Some of my questions were already answered, but can we talk a little bit on -- can we defer to slide CE-5? I wonder if the sponsor and the FDA looked at COA data beyond week 25 to see if the profile changes over time.

MR. RICHARDS: In terms of range of motion, I'd like to invite Dr. Shuster to speak to this point.

DR. SHUSTER: Dale Shuster of Daiichi Sankyo. The answer is yes. We have collected, and continued to collect, COA data on this study. And after week 25, we have some of this graphed here. This is looking at the mean change from baseline, and in the range of motion, you see week 13 as when

we assessed the mid-point of this study. The final assessment for part 1, the primary analysis endpoint is week 25, and we've continued to follow patients.

DR. HALABI: Were you able to do this by responder versus non-responders? Do you have the data?

DR. SHUSTER: We have the data. I'm not sure -- I think you mean is the range of motion different by whether a patient responded or not responded.

DR. HALABI: That's correct.

DR. SHUSTER: I'm not sure if we have that data. Well, we don't have the analysis. I should say we have the data and we can look at that.

DR. HALABI: I guess, then, the question will be back to Dr. Fiero from the FDA.

Similar to slide 20, I'm curious if you have looked at the data beyond week 25, knowing that, obviously, this is exploratory, but I'm just curious

DR. FIERO: That's a good question. We did

not look very closely at the data during the open-label phase simply because when patients are unblinded to treatment, we know that it could potentially affect the estimates. So we focused on the double-blind portion of the trial.

DR. RINI: Dr. Klepin?

DR. KLEPIN: Heidi Klepin, Wake Forest. I wanted to circle back to the issue of safety and hepatotoxicity specifically, and I wanted to see if you could provide any data around observations for characteristics at baseline in particular that might have been associated with hepatotoxicity, so things that were already touched on like comorbid conditions, age.

I did read in the provided materials, I think there were only 8 patients over 65, and half of them had a treatment-emergent adverse event. So there's something there but too small to maybe make much out of.

Then I think the other issue that came up earlier were concomitant medications. So particularly as we think about how this drug would

be used chronically in patients over time, it's not just a static baseline characteristic, but you're going to have patients who are on this drug who then start atorvastatin, or who then have a new comorbid condition.

So the more we can understand from your data now to try and make some judgments around that, that would also help providers. Then of course, the registry as proposed is going to be really an important part of that as well if that moves forward.

MR. RICHARDS: Sure. I'd like to invite Dr. DeLeve to talk about the risk factor analysis that, unfortunately, wasn't able to identify any particular risk factor that was predictive. As you've noted, the patient registry is hopefully going to help us a lot with understanding that going forward that is the function of it.

DR. DeLEVE: Laurie DeLeve, University of Southern California. This was analyzed in the TGCT population because it's much more difficult to locate a non-TGCT cancer population. They looked

at gender, prior therapy, medical history, including baseline liver and renal function, as well as alcohol use, hepatitis, and no independent risk factors were identified.

DR. KLEPIN: In the medical history, were there any specific things like diabetes or other diseases that were looked at, or a comorbidity scale, or something of that?

DR. DeLEVE: Nothing came out during the analysis.

DR. KLEPIN: Okay. But they were looked at.

DR. DeLEVE: They were looked at.

DR. KLEPIN: And medications were also collected and looked at?

DR. DeLEVE: Medications were -- yes.

DR. KLEPIN: It would be nice to see reported somewhere.

DR. RINI: We're running a little behind, and I still have a list of people with questions. What we're going to do now is take a 10 minute break -- not a minute more -- and then come back. We'll do the open public hearing, and then we'll

have another 10 or 15 minutes of questions to the sponsor before we do the discussion and vote.

So it is now 10:27, so we'll start again at 10:37. Thank you.

(Whereupon, at 10:27 a.m., a recess was taken.)

Open Public Hearing

DR. RINI: 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 known, 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 at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise if you do not have any such financial relationships. If you choose not to address this matter at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues 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 myself, and 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 are representing, for the record.

DR. TESLER: My name is Dr. Peter Tesler. I'm not representing any organization. The sponsor covered my expenses in connection with my appearance today, and I have no other financial disclosures to report.

Shall I proceed?

DR. RINI: Sure, please.

DR. TESLER: I finished my pediatric residency in 1992, and I've spent most of the past 25 years in medical leadership positions with direct responsibilities for quality of care and patient safety. Today, however, I am here as a patient. I started to have vague right knee pain in the summer of 2014 and saw a physician in early fall. I was diagnosed with diffuse TGCT or PVNS in November 2014. After receiving this diagnosis, I started scouring the web for treatments. Aside from surgical resection, there were not many options.

By the spring of 2015, I was steered to an orthopedist at Memorial Sloan Kettering who suggested that in my case there was only a 50 percent chance that surgery would be curative. I was referred to Dr. William Tap, who informed me that there was finally a promising medical treatment on the horizon, a new drug that was in phase 3 trials.

My PVNS was progressing, both by MRI and more importantly by my symptoms: pain, swelling, and decreasing mobility. I eagerly signed up for the trial and unfortunately ended up in the placebo arm for 6 months. My symptoms continued to worsen, and pain and decreasing mobility became a daily fact of life.

By the end of the placebo arm, my walk had turned into a limp, stairs were truly problematic, and I could no longer put on my right sock. At that point, I knew I was weeks away from requiring a cane. Needless to say, this deterioration had dramatically impacted both my professional and personal life, and that of my family as well.

I finally entered the treatment cycle in April 2016, almost a year and a half after diagnosis. My response to pexidartinib has been life changing. After few months on the drug, I was able to walk without pain or limp, and after a bit longer, I could easily go up and downstairs and even bicycle once again. In the fall, I could actually run, something I had not been able to do for almost two years.

Fast forwarding to this past January, I climbed Machu Picchu with my wife and three sons, something I would never have envisioned prior to starting pexidartinib. However, I am by no means tumor free, and my tumor mass, after a significant reduction, has mostly plateaued over the past 6 to 9 months. I know I will be on this drug, or a variant, over the long term.

So to be clear, I am fully advocating that this committee and the FDA approve pexidartinib. It currently is the best pharmacologic treatment option, and although there are other drugs in the pipeline, your approval can make an immediate and

profound impact on all TGCT patients, and no patient will have to needlessly suffer for waiting and hoping to find a trial. I appreciate how lucky I have been, although aghast at still being on protocol for over three years. My 20th MRI is scheduled for June.

Putting on both my physician and patient safety hats, pexidartinib is not without side effects. Although my hair did not go shock white as promised, and I had no signs or symptoms of hepatotoxicity, the most significant side effects for me have been GI, fatigue, and occasionally not feeling as sharp as I would like.

I've had the option to decrease the dose to address these side effects, but given the trial status, if the tumor mass had started to increase, I would be denied the ability to return to the prior higher dose, which is of course no choice at all. If this drug is approved, then wise clinicians like Dr. Tap can adjust dosing strength and schedule, and presumably work out a therapeutic regimen for PVNS patients.

Prior to approval, the options are extremely limited, and no patient with this disease should be faced with those choices. Therefore, I implore this committee to move forward and approve pexidartinib so that every patient in the United States can have this treatment option without further delay and have the chance to regain their lives and live to the fullest with all this drug has to offer. I thank the committee for your time and attention.

DR. RINI: Thank you. Speaker number 2 can step up and introduce yourself and any affiliation.

DR. SRINIVASAN: Thank you for the opportunity to speak today. My name is Dr. Varuna Srinivasan. I'm a physician with a masters in public health from Johns Hopkins University, and speaking today as a senior fellow at the National Center for Health Research, which analyzes scientific and medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug and medical device companies, so

I have no conflicts of interest.

We have several strong concerns about the drug pexidartinib. About 1.8 per 1 million persons will develop GCTTS, and 9.2 per 1 million persons will develop PVNS. These rare forms of cancer are benign with a very low chance of becoming malignant. However, patients often experience a debilitating quality of life with reduced range of motion. Currently, radiation therapy is shown to be beneficial in preventing cum recurrence in infiltrative cases when surgery is not possible.

When looking at the drug in question today, it is more important to focus on functional outcomes and what it means for patients rather than overall response rate or decrease in tumor volume. It appears that while this drug offers modest functional improvement on average, there are major risks. Almost half the patients dropped out mostly due to liver injury and liver failure. We agreed with the FDA that there is a lack of understanding on the long-term effects of this drug on those injuries.

The big picture is important. These cancers typically affect people between ages 20 to 40. Should such young patients be exposed to the risk of liver failure in order to possibly have a small short-term decrease in tumor size or a little more than 10-degree allowance in range of motion?

In the pivotal clinical trial conducted on this drug, 38 percent of patients showed an overall response rate after 6 months, but close to 90 percent had elevated liver enzymes within the first 2 months of treatment, for the scrutiny reveals that the recurrence rates were not studied, and while patients' liver enzymes were monitored regularly, the sponsors failed to adequately characterize which patients would be more at risk for liver failure or injury. The sponsor also did not determine for which patients the side effect of livery injury would be irreversible.

As we all know, there is more monitoring in a clinical trial than in the real world of medicine, where the expertise of physicians and the understanding of patients varies widely, and yet

the sponsor is proposing the same monitoring strategy as part of their REMS. If monitoring is less stringent than in the clinical trials, the incidence of liver failure cases could be far worse in a real-world setting.

Furthermore, this tumor has a highly heterogeneous histology, and some of the patients in the pivotal trials had previous systemic therapy. As a result, the target population for whom this drug would be the most beneficial has not been established.

This tumor is non-lethal, and the persistence of this tumor does not lead to malignancy, so we ask again that you consider whether the high rates of liver injury are really worth the risk. The bottom line is that it is not known how many patients would develop irreversible liver injury from this medication. Merely establishing a basic patient indication profile with moderate REMS strategy does not guarantee a positive risk-benefit profile.

I hope that you will agree that better

clinical studies that accurately evaluate the functional efficacy outcomes, as well as the safety profile of this drug, are needed before approval should even be considered. We urge the committee today to consider these important points while discussing and voting today. Thank you.

DR. RINI: Thank you. Speaker number 3?

MS. ROWE: Hi. My name is Angie Rowe. I'm the executive director at Global Genes. We do receive corporate donations and grants, including from Daiichi Sankyo, who paid for my travel and expenses to be here today. I have no financial interest in the outcome of the meeting today.

Global Genes is a leading rare disease patient advocacy, nonprofit organization whose mission is to connect, empower, and inspire the rare disease community. We envision a globally connected community equipped to eliminate the challenges of rare disease. With an international scope, Global Genes develops educational resources, programs, and events that unites patients, advocates, and industry experts.

At Global Genes, we are very passionate about the work that we do for the patient community. There are more than 7,000 rare diseases affecting 30 million people in the United States, and 350 million people globally. Only 5 percent of rare diseases have an FDA-approved therapy. There are no cures.

At Global Genes, we want to encourage and support the development and approval of treatments for rare disorders. Options and choice; these are things that are as rare as the disorders many people face. Through our work at Global Genes, we see story after story of rare disease patients that receive a therapy to go on to do remarkable things with their lives, and more importantly have a much improved quality of life.

Patients can tell their personal journeys, however, representing thousands of patient communities and working with them on a day-to-day basis, not in clinical or medical settings but on an emotional and support level, the burden of a debilitating, rare disease with a small patient

population and limited support networks leads to a lot of quality-of-life issues. There are things like chronic pain, loss of work, and long-term medical expenses to name a few. The emotional and physical toll is not just on the patient but on the caregiver.

This long-term quality-of-life burden cannot be underestimated and is why I'm here to give all those affected by rare disease and disorders a voice in the process. We want to continue to support in any way that we can options and choice to improve the quality and length of life for everyone battling these rare conditions, as well as their families and caregivers.

Thank you to the FDA, committee members, and most importantly, the patients and caregivers for your time here today.

DR. RINI: Thank you. Speaker number 4?

MS. MERCADO: Hi. My name is Rhoda, and I'm from Chino, California. I'm a patient here. I'm not being paid to come here, but sponsor covered my expenses for my accommodations, and I don't have

any financial relationship with the company.

Before I started this medication, my life was in constant torture because of the severe pain and limited mobility. I have a diffuse PVNS on my right knee, and it evolved slowly. Years prior to my diagnosis of PVNS, I was diagnosed with osteoarthritis of the right knee. That's when I was beginning to have pain and swelling. I thought, I just have arthritis, but the swelling and pain didn't go away. Instead, it became more painful and very swollen.

I went to see another doctor who said that I have PVNS, and I was referred to an orthopedic oncologist. My knee was hard like a board, swollen, with very severe pain, waking in the middle of the night crying because of the pain.

I'm a registered nurse by profession, and I work as a staff nurse in an acute hospital and constantly on my feet 12 hours a day. I continued working even though I was in pain and can barely walk because the doctor I was seeing at the times said he will amputate my leg.

I was praying that there's a study out there to help me cure this disease, so I will be relieved of my pain and suffering, and save my leg. Faith brings me to this study. I was lucky that my doctor referred me to another doctor, and then I got to the trial study.

I want to fight. I don't want to give up. If I lose my leg, at least I tried my best, and if it was meant to be, at least I tried my best. I was very blessed to get on this trial medicine that has helped me a lot to get better and that someday can help other people like me suffering from PVNS.

Before starting with my trial medicine, I was already on three narcotic medications that was not helping with the pain, and I was walking like a kangaroo. I can't stand or bend my knee, limping while walking, and I was still working.

After I started with my medication, my severe pain from 10 went down to 7 within a week, and my knee started to soften. I went on medical leave after the first week that I started my trial, continued my medicine, and continued to see my

trial doctor, which is Dr. Singh [ph].

After 3 months, I was back to work without restriction as a registered nurse. I can bend my knee. My pain is very minimal, just at the end of my 12-hour shift. The swelling is down and my mobility is back. I just refrain from running because part of my bone became thin because of the tumor that invaded my bones.

I was able to keep my leg in one piece, no amputation done. I am back to being a normal person. The side effects were minimal, like my hair started to grow gray, and my skin color is lighter. When my coworkers saw me back to work, they call me, "Rhoda, you're a miracle." They are the people that kept seeing how much I suffered from PVNS.

This medication can help a lot of people suffering out there from losing a part of their limb and will have mobility and better quality of life. I've been on this trial for more than 6 years, and I hope this medication will be approved. I don't want to be back to the suffering

again, pain and lack of mobility, and no quality of life. I thank the committee for giving me the opportunity to talk here.

Clarifying Questions (continued)

DR. RINI: Thank you.

The open public hearing portion of this meeting is now concluding, and we'll no longer take comments from the audience. As promised, we're going to do just 10 or 15 minutes to finish up with questions to the presenters before we turn to the panel discussion and voting questions.

Dr. Uldrick is up first.

DR. ULDRICK: Thank you. I wanted to go back to slide CE-16 from the sponsor. Now that we'd have the opportunity to look at the reasons for missingness, if you could go through the methodology for the sensitivity analysis for the PRO endpoints, that would be very helpful.

MR. RICHARDS: I'd like to invite Dr. D'Agostino to walk us through some of the sensitivity analyses in order to account for the missingness.

DR. D'AGOSTINO: Good morning. Ralph D'Agostino. I'm a professor of biostatistics and data science at Wake Forest University, School of Medicine, and I'm the director of our biostatistics shared resource at our comprehensive cancer center. I'm here today as a paid consultant with the sponsor, but I have no financial interest in the outcome of this meeting.

Let me begin by saying that I have thoroughly reviewed the efficacy and primary/secondary efficacy data from this trial and also the sensitivity analyses that have been described in your briefing book. Before I go to the answer to your question, I just want to say, based on my review of the sensitivity analyses, I do believe that the efficacy results that we've been shown, that were both in your book and also in the slides today, are both robust and credible, and that the results are both clinically meaningful and statistically significant, even in the presence of the missing data that we've observed. So let me just go through some of this now with you all.

I'm going to first talk a little bit about the tipping-point analysis for range of motion, but we can also talk about the other PROs because I think you might have been interested in both. There were three separate sensitivity analyses performed to identify what could be the potential impact of and missing data.

The tipping-point analysis is the most conservative, and the FDA statistician, Dr. Fiero, also showed this. This is an analysis where the data with missing values in the treatment group would have a penalty assigned to them. You would impute a value and then you would subtract or penalize the data a certain amount.

If you walk through this table, what you will see is, in order for the statistically significant results there were observed in this dataset to become non-significant, a penalty by the sponsor's calculation of minus 16 percent, which would be a 24-degree worsening in range of motion, would have had to be assigned to each of those patients who had missing data due to adverse

events.

What that is saying is not only did patients not get better, but they'd have to get clinically meaningfully worse if they had dropped out of the study.

Now, the FDA statistician, she presented at 12 percent, which was, I believe, a blended calculation between patients who dropped out due to adverse events and patients who dropped out for other reasons. But even at 12 percent, if we all recall the figure she showed, the curve would have had to go below -- what essentially this is saying is in order for the results to become statistically non-significant, you would have had to show worsening, clinically meaningful worsening, 12 percent, what would be essentially an 18-degree worsening of what would have been anticipated to have occurred. I think that's the first point.

The second point is that the effect size or the difference that was described by the FDA in their document and elsewhere, of saying that the clinical improvement ranges between 7 percent and

19 percent for range of motion -- now I'm focusing on -- just again to put that into perspective, recall that the 7 percent reflects a 10-degree improvement in range of motion.

Now that lower bound was established because of the tipping point analysis. The actual observed data or the average effect size is somewhere between 20 degrees, up to as high as 29 degrees.

DR. ULDRICK: So you only looked at that specific analyses and not the other analyses in your sensitivity analysis; is that correct?

DR. D'AGOSTINO: So we can --

DR. ULDRICK: I know we're on time limitation --

DR. D'AGOSTINO: Sure. If you want to put up the other two sensitivity analyses. You're referring to the other sensitivity analyses.

DR. ULDRICK: Are these all range of motion or about something else?

DR. D'AGOSTINO: Do you want to see PROMIS, right, as well?

Can you put up the PROMIS slide? The PROMIS

data also was very promising. It was also highly statistically significant. If we look at the PROMIS data here for the range of motion -- I'm sorry, the PROMIS data for the tipping-point analysis, what you can recall for the PROMIS data is that data was observed or measured at 3 time points, baseline and then at 9 weeks, 17 weeks, and 25 weeks.

One thing that also may not have been clear is when there's talk about missing data, lots of individuals had data at intermediate time points and just not the final point time point. The analysis of the tipping point, which you see in this figure here, the boldface minus 3.5, minus 3.6, that is saying that the penalty on the PROMIS scale, that would have had to be assigned to people with missing data, was between 3.5 and 3.6 points at each time they were not observed.

So if someone had missing data at 3 time points, this penalty would have been assigned sequentially 3 times, essentially a cumulative 10-point effect.

Again, why I as a statistician believe that this is data which suggests that the results are robust and strong is because in order for this to have occurred, the patient would have sequentially been getting worse and worse and worse at each time point, at basically a 4-point scale, which Dr. Bernthal had already told us that, essentially, a shoulder surgery worth of pain would have to get worse each time, subsequently.

This is PROMIS data, and again, the data was very strong and compelling.

DR. ULDRICK: Good. Thank you. That answers my question.

DR. RINI: Thank you. Dr. Lewis?

DR. LEWIS: It was answered.

DR. RINI: All set? Dr. Strader?

DR. STRADER: I have a question about the response to the hepatotoxicity. I saw somewhere in the data that the drug would be discontinued, blood work would be performed weekly, and then the drug would be restarted at a lower dose.

So the question I have is, is there any data

to suggest that this lower dose, dropping the drug by 200 milligrams I think it was, shows any benefit whatsoever? Because we want to be sure if we're trying to do something to mitigate the risk, that we're also not doing something that's going to be clinically meaningless because you've not studied the treatment at 600-milligrams a day. You've only studied at 800 and 1000 milligrams a day.

So is there any data that suggests that dropping that dose has any clinical benefit whatsoever?

MR. RICHARDS: We do have on two fronts the case that Dr. DeLeve demonstrated, that at least anecdotally, we know that dropping the dose can lead to the decreases in ALT/AST in terms of efficacy, which is really primarily your question.

We have very few patients -- I believe we had 11 on the randomized portion, and what we show within them is that these patients, none of them regressed [indiscernible]; we know that. They do continue to have decreases in tumor size that's an extreme convenience sample. So it's a bit

difficult to do a subgroup analysis. But they did continue to show tumor regression in the patients that continued on, for example, 600 and 400 milligrams.

DR. STRADER: Okay.

DR. RINI: All set? Dr. Hunsberger?

DR. HUNSBERGER: Yes. I want to go back to the missing data one more time and the reasons for the missing data. There's a difference between compliance and not getting the outcome data. Some of the reasons were severe adverse events, so I'm not clear why you still couldn't get the primary -- or the endpoints, even though they maybe came off treatment.

So was it protocol specified that if they had a severe adverse event, you wouldn't get that endpoint or -- I just wasn't clear on the reason.

MR. RICHARDS: I'd like to invite Dr. Shuster to speak to that, the context and how that data was collected in those particular patients.

DR. SHUSTER: Maybe just to start with this

slide for the -- Dale Shuster of Daiichi Sankyo. To start with the slide on disposition, as you said, many patients came off on the pexidartinib arm due to adverse events. Several of these occurred very early in the study treatment. As you surmised, the protocol then did not continue to follow those patients. Many of them would pursue other options at that point anyway.

DR. HUNSBERGER: So that was according to protocol or they just decided I don't want to be part of this study anymore?

DR. SHUSTER: It was part of the protocol. We didn't ask do you want to continue with the assessments.

DR. HUNSBERGER: Okay.

DR. SHUSTER: On the placebo arm, you'll note, though, that's withdrawal consent, so that's getting out of the protocol.

DR. RINI: We have time for two more questions. Dr. Villalobos will go first. We'll keep it short and to the point.

DR. VILLALOBOS: Yes. Dr. Villalobos from

University of Denver. This question's for Dr. Bernthal, and I just want to quickly address if you can comment on the risk of a large joint total replacement on morbidity and mortality of those procedures.

MR. RICHARDS: Dr. Bernthal?

DR. BERNTHAL: Nick Bernthal, UCLA. The short answer is that total joint arthroplasty is one of the most successful interventions we have, by and large, in healthcare. A total joint replacement is a very good surgery.

The challenge in this disease is that the total joint replacement is actually not the real driver -- you're not solving the patient's problem. You're addressing the underlying arthritic where of chronic inflammation in the joint. The tumor is in the surrounding tissue, so it's creating inflammation that is eroding bone, and you're replacing the bone in the total joint replacement. But to get the tumor out, you're doing a massive resection of the entire capsule of the knee and of the surrounding tissue.

So to answer your question, in split terms, the risk profile of a routine total joint replacement is very favorable; 98 plus percent of these patients do very well. Total joint replacement in the setting of tenosynovial giant cell tumor, when the tumor is much more than replacing the bony context itself, it's quite dramatic. So taking all of that out, we have dramatically increased rates of stiffness, infection, and bleeding. You have very little soft tissue to close over the implant, which often leads to skin over metal, which is a disaster from our end long-term outcomes.

So while it's a rare disease and I can't hang my hat on numbers, I can tell you anecdotally that these dramatic cases, total joint arthroplasty, has a much higher rate of complications and problems, and I'd encourage the committee to weigh that against the risk-benefit profile of the drug and not simply the drug in isolation.

DR. RINI: Thank you. The last question

from Dr. Calis.

DR. CALIS: Karim Calis from NIH. My main question was about the missingness, but I think that has been addressed as well as it's going to be. The other question I had was with regards to slide CE-13, where in the assessment of the primary endpoint, there was 20 percent in each group; that the primary endpoint was not evaluable.

I understand we're dealing with diffuse disease and maybe complexity there, but can you explain what not evaluable was it, because it couldn't be quantified?

MR. RICHARDS: I'd like to invite Dr. Shuster. As he approaches, these non-evaluable were considered non-responders of the analysis. But in terms of why they were non-evaluable, I'll let doctor Dr. Shuster speak.

DR. SHUSTER: Dale Shuster, Daiichi Sankyo. These are non-evaluable. This, as a reminder, is a time point assessment at week 25. Most of these patients are patients who had discontinued. You remember that there were 20 patients that had

discontinued. There were two other patients that were not evaluable. The scans were not assessed. But the majority is they just didn't continue in this study long enough to have an assessment.

Questions to the Committee and Discussion

DR. RINI: Thank you.

I will now proceed with the discussion questions to the committee and panel discussions. I'd 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, and if you could pull up our discussion question, which is our only question.

Discuss whether the benefits of pexidartinib, as characterized by a clinically meaningful reduction in tumor burden and an improvement in range of motion, outweigh its risk of hepatotoxicity. I think probably the main items to discuss are the -- I know the FDA is interested in the indication wording around this condition associated with severe morbidity or functional

limitations and not amenable to improvement with surgery; some of the missing data that's already been discussed and then hepatotoxicity. And I think Dr. Nowakowski wanted to lead us off.

DR. NOWAKOWSKI: Thank you. Greg Nowakowski, Mayo Clinic. I think it is clearly a very active compound. The single-agent response rate is impressive. In addition to response rate, if you look at the waterfall diagram, it appears that the majority of the patients do have some shrinkage of their tumor, so there is no question of activity here in my mind. It's an active agent.

Although the functional data and the COAs had limitations, which Dr. Fiero very nicely presented from the FDA, I could not help thinking that shrinking of the tumor itself must translate into some clinical benefit. Although we can have the discussion about the degree of this clinical benefit, typically in this setting, the shrinkage of the mass would be associated with clinical benefit in terms of the function.

I think where my problem is and where I

would like to focus is basically toxicity, liver toxicity, because the TGCT is not fatal typically, but liver failure can be fatal. We have seen the liver toxicity is a significant problem associated with this compound.

The REMS program, which is proposed by the sponsor, is going to be somewhat difficult to institute because a lot of patients have liver function test elevation with this drug, and really the threshold for stopping it or adjusting depends on the levels of the enzyme. The education will have to be done of the prescribers, and I'm glad to see that only the certified providers will be able to prescribe it.

My question actually goes to FDA a little bit, and it's more of a policy question. How do you define success of the REMS program, in general, in the future? Let's imagine ourselves that this drug gets approved, and the sponsor has the database, clinical database, and comes back after a period of time, and there are 150 patients in this database. There was one patient with prolonged

liver toxicity which recovered and one with liver toxicity which led to death, maybe related to liver toxicity or maybe to some other complications.

So you have 2 out of 150. What do you do? How do you make the decision that REMS program, which you have in place and was proposed by the sponsor and agreed on, is successful moving forward?

DR. FASHOYIN-AJE: We'll defer response to that DRISK team.

DR. LaCIVITA: Hi. This is Cynthia LaCivita with the FDA. The success of the REMS program is still a discussion that we're having within the agency. There are certain things that we can look at. We can look at process metrics to determine whether all the prescribers are enrolled in the program. We can also look at outcomes, too. I think part of the registry would be to collect some of that information to determine how successful we are with monitoring and things of that nature.

DR. NOWAKOWSKI: To follow up on this, is there a specific threshold in bad outcomes? Would

you consider using those, or does someone move the target depending on the denominator?

DR. WARD: The exact threshold is still under discussion. But yes, the idea would be that we would use the registry in combination with probably a postmarketing requirement to look at the safety data over a period of time that will be defined. If we are seeing liver toxicity rates that are higher, substantially higher, or -- the exact numbers are under discussion, but the idea would be that if we're seeing toxicity that is at a higher frequency or more severity than we observed on the clinical trial, we would take additional action.

DR. NOWAKOWSKI: Just for my own education, from your experience of other programs, how real time is it? Is there a significant delay before you get the data? Do you get it in batches or does it come on the real time, it's program dependent?

DR. FASHOYIN-AJE: I think it's variable. The timeline for getting the data is also still under discussion, and we have several proposals

that we're internally discussing.

DR. NOWAKOWSKI: Thank you.

DR. RINI: I just have one quick follow-up to that in terms of you said the thresholds are under discussions. Is that all defined a priori to anybody enrolling, or is it an ongoing assessment as you move through this registry?

DR. FASHOYIN-AJE: Well, it can be both. We anticipate having some a priori guidelines. But I think it's also important to keep in mind that there are a couple of different potential things that we can be looking at with the REMS. The first would be whether or not patients are following the label instructions, and if that is not the case, then there may be labeling implications.

The second would be that if patients are following the label, and there are label instructions and there are no additional risk mitigation procedures that we can identify but the risks -- I think we tried to make it clear that the long-term risk is still uncertain. So if we get more information about that long-term risk that is

not necessarily mitigatable, then we could always take a different regulatory action.

DR. RINI: Ms. Broyles, did you have a comment?

MS. BROYLES: I was just curious. I've listened, and certainly the public hearing portion was really wonderful to have a patient describe what they'd been through and the toxicities or not. There is apparently a dramatic response in some of the video, but I guess the -- I'm not really seeing how quick the symptoms come back after they stop the drug if they have to get off the study for any reason whatsoever.

But as far as the risk, I mean, most of these patients, the burden of living with this every day, I think we can't overemphasize the poor quality of life that they go -- I mean, everything is impacted by this disease. And it doesn't matter where it is, the impact is severe when it gets to that point. and I know a lot of them have been told about the hepatic toxicities, but many of them are at the point where they're willing to take that

on. That's all.

DR. RINI: Thank you. More discussion around hepatotoxicity; Dr. Strader, anybody want to comment?

DR. STRADER: Sure. Dr. Strader, University of Vermont. We do these consults for liver toxicity all the time. The first thing I want to say is elevations in AST and ALT are not liver failure. It is increased in aminotransferases. It's inflammation in the liver. It's not liver failure.

That said, though, the majority of people, or patients in this study, 90 percent or so had increases in their AST and ALT. So they had some evidence of inflammation in the liver, but it doesn't appear to be liver failure in that 90 percent of individuals.

Then the question as a hepatologist I would ask at this point is how high are the liver enzymes? The FDA appears to be willing to tolerate less than 3 times the upper limit of normal, and according to Dr. DeLeve, 40 was considered normal.

So if your ALT 119, go ahead, you can start the drug again.

It's probably okay if it's just AST and ALT elevation. These people would have to be watched. That's why not only the risk mitigation, but in my opinion, the follow-up of these patients is necessary. So if you've got a patient with an AST or ALT or 119 and continuing on this drug, you need to follow them on a regular basis to make sure things don't get worse.

The other issue is, is the benefit of the drug worth the risk of the toxicity? We do this all the time. I see patients coming in all the time who are on their statins, and their AST and ALT went up, and everybody's waving their hands and very excited. But the issue as far as most hepatologists are concerned is it is better -- it is easier for the patient to tolerate elevations in AST and ALT than to have a heart attack or a stroke. So you say continue it and just monitor.

So the question is, where are we with this drug? Does this drug benefit these patients or

not? And it appears that the tumor gets smaller and that there's some change in range of motion. What I'm struggling with is the clinically meaningful benefit.

We've had a couple of patients here who say that they have had some clinically meaningful improvement, but the question in my mind then becomes what happens over time? We're talking about giving this to these patients for the rest of their lives. So that means is it 6 months of benefit, at which point nothing gets any better after that, or is it a continual maintenance of whatever benefit they have now for 20 or 30 years, or do things get worse?

In the meantime, as was mentioned earlier by Dr. Klepin, these patients age. They become diabetic. They get high blood pressure. They get heart disease. They start on other medications. That in combination with pexidartinib may increase their risk for liver related injury.

So it's a very sort of complicated question to answer, the AST and ALT elevation in and of

itself. The bilirubin thing is different. I think they're doing the right thing. If your bilirubin goes up, stop the drug. Sorry. But the AST/ALT is a different situation, and the question still is, is the benefit of a decrease in tumor size and a little bit of increase in range of motion, with or without really clinically meaningful improvement and change in pain, worth the AST/ALT increase?

It may be, but in my opinion, that means a lot of follow-up is going to be necessary, and a lot of monitoring is going to be necessary in these patients because we're tolerating a moderate ALT/AST increase over a very long period of time. So I think that these patients should probably have liver tests done beforehand, and probably not just liver tests. We're talking about people in their 20s and 30s, so they may be at risk for other things.

So maybe if we're talking about AST and ALT of greater than 40, maybe they should all have their autoimmune serologies tested and make sure they're all vaccinated against hepatitis A, B and C

before starting, so we know there's no underlying possible autoimmune condition, and they've all been vaccinated, and then begin and monitor them on a regular basis so that we can be sure that we're not -- if we decide that this drug should be approved because it is important that people not be miserable for the remainder of their lives, but that we're not cavalier about exposing them to a drug over time that may cause some benefits in the future.

DR. RINI: Thank you. Other comments about hepatotoxicity? That was great.

DR. VILLALOBOS: On that note as well -- this is Victor Villalobos, UC Denver, I think we can't necessarily take the toxicity of this drug in a vacuum. There is significant morbidity and mortality from these procedures that we have to expose these patients to, not including increase of being sedentary over the course of her life because they can't be active. So weight gain, risk of DVTs from not being able to move correctly; postoperative complications, risk of infection.

These are larger surgeries, typically, and you're talking about sometimes multiple, multiple surgeries. So I think we can't take this all without consideration of the actual disease process itself. This is not a disease that's going to get better on its own, and oftentimes people will be living this for 50-60 years.

Now, the implications of how to use this drug I think are still not clear, and I'm not sure that they will ever be clear based off of a study. And it may very well be that you treat a patient for 6 weeks or 6 months, they recover, respond, and based on the data we have on this trial, 25 weeks, 0 patients progressed on a placebo arm.

So it may be that only short periods of treatment over time may be as efficacious. Now, We don't have that information, but we will not be able to get that information unless we do a larger study with a very extremely rare subtype of tumors that would be eligible for this particular drug itself.

DR. RINI: Thank you. Maybe just finally,

we can lean on our statisticians or patient-reported outcomes because there's been a lot of discussion about how meaningful is the range of motion data, et cetera. So I don't know if anybody has comments about missing data in the sensitivity or tipping analyses or just the PROs in general.

DR. HUNSBERGER: I think it really is important to take the sensitivity analyses into account because given the discussion of the missing data, it did appear to be patients who were either not having an effect and having adverse events so they couldn't take the drug, and that is a biased estimate if you ignore the people who had missing data. So we can't take that as the best estimate of the effect.

I think the sensitivity analysis do show that even if we put in reasonable or extreme estimates of worsening effects, you still get a benefit. So I think there is a benefit on the endpoints. I can't really say whether they're clinically meaningful, but one of the presenters

did talk about going from not being able to stand up to being able to stand up.

If we could have had an endpoint that looked at the proportion of people who couldn't stand up and then could stand up, that would be really helpful as far as a clinically meaningful outcome, but I don't think you did that analysis. But that would be the kind of thing that would be really helpful, if you could look at the data and say, rather than range of motion, how many people could not stand up and then stand up? And I think that --

DR. CRISTOFANILLI: But they I think we have two different issues. One is the magnitude of benefit that we cannot quantify because of the deficiency of the study. The data is not there.

DR. HUNSBERGER: Right.

DR. CRISTOFANILLI: Of course, is you have a response, they would say, supposedly you have an improvement in your symptoms. But the data is missing, so we cannot, based on the data of this study -- even with the sensitivity analysis, we

extrapolate. We want to believe that this is the case.

DR. NOWAKOWSKI: To be honest, I prefer it this way. Having seen the responses, objective responses, they may be missing some of the data in the functional assessment than the other way around; not having responses and having some improvement in functional status, because then you really question a lot of those tools. Those tools are not really well developed.

DR. RINI: Other comments?

MS. PREUSSE: Courtney Preusse, consumer rep. There's been a lot of talk around the missing data, and that being the result of worsening patient outcomes. But isn't it possible that the missing data is a result of these patients resuming their normal lives and not being focused on the study anymore, and actually going out and having an improved quality of life?

DR. RINI: I think there is concern either way that it's missing because they're so much better or it's missing because they're so much

worse. But I think, as was stated, it's just missing. At the end of the day, it's just missing.

Do you have a comment?

DR. HUNSBERGER: Except if you looked at the table for missingness, it was always because of severe adverse events, which meant -- the sponsors said that meant they went off treatment; they tried other treatments. So it was getting worse. If you looked at the reasons, it was for worsening.

DR. RINI: Other comments over here?

DR. LEWIS: Just looking at these kind of PROs, when patients are doing well, that's when they reply. When patients aren't doing well, that's when they tend not to reply, just historically.

I do have one question about the registry. Who's going to be monitoring the registry? Because it seems like it's great that all these patients will be put in a registry, but who will be following it and managing it over time? Is it the FDA or is it the company?

DR. WARD: Typically, the company is the one

that's running the registry and they provide specific pieces of data to the FDA as prearranged.

DR. LEWIS: Will you monitor it and then refer to the physicians should untoward events be happening as well?

DR. WARD: Yes. The purpose of the registry is primarily to collect data and to make sure that we're collecting data from all patients that are receiving pexidartinib. So one of the limitations of the adverse event reporting system that is used across the country is that we don't have a denominator for patients. So when we get adverse event reports, it's difficult to know what the frequency of those adverse events are in the population receiving a drug.

One benefit of the registry is that it allows us to register all patients receiving pexidartinib so that we can gather data about liver toxicity. The registry will prompt the physician to gather specific pieces of data and submit that to the company on a periodic basis, and that is all defined, would be defined. The company will gather

those pieces of data and then provide reports to the FDA on a prespecified schedule.

DR. RINI: Thank you. I'm to remind you to state your name before you speak for our transcriber. Thanks.

DR. STRADER: I beg your pardon. Doris Strader. I just wanted to know how long is the registry? Is it 5 years, or 2 years, or do we know long?

DR. WARD? Sorry. This is Ashley Ward from the FDA. That was me before as well. Those details are still being worked out.

DR. LEWIS: Val Lewis, MD Anderson. Is it a possibility the registry would be shorter than the people on the drugs; so if it's a 2-year registry but you have people on it for an indefinite amount of time?

DR. WARD: Well, people could be on the drugs for a lifetime, and I don't anticipate the registry lasting for an entire lifetime. So we expect the registry to last as long as it is necessary and to gather the information as

necessary to make an informed decision.

DR. LEWIS: So what will be the mechanism for monitoring for late effects? What if it does nothing in the first 2, 3, 4, 5, 6 years, but then people will be on it for 10, 12, 13 years; who will be monitoring for the late effects, then?

DR. WARD: Again, this is Ashley Ward from the FDA. Like I said, the specific details of the duration of the registry are still being worked out through the review cycle, but the intention is to capture patients who have long-term sequelae from the hepatotoxicity.

DR. LEWIS: [Inaudible - off mic].

DR. RINI: Your microphone.

DR. LEWIS: So it would be longer than 5 years; Val Lewis.

DR. WARD: Ashley Ward from the FDA. It's not been determined. I anticipate that it will be longer than 5 years.

DR. RINI: Okay. Other comments around anything we've discussed or anything that's been presented for discussion?

(No response.)

DR. RINI: FDA, anything else you need discussed?

DR. FASHOYIN-AJE: This is Lola Fashoyin-Aje. Just to follow up briefly on an issue that came up, which was, are there any data to support starting at a lower dose and then escalating to mitigate the incidence of aminotransferase elevations, the sponsor responded and stated that approximately 11 patients had this experience of a lower dose and that those patients continued to regress.

I wanted to state for the record that that characterization seems to be a bit generous. I think that what we can say is that those patients did not progress. I don't know that we can say that there was regression at the lower dose.

DR. RINI: Courtney?

MS. PREUSSE: Sorry. One last quick question, point of clarification so that I understand. Courtney Preusse, consumer rep. The only data that I see around non-recoverable her

about her hepatotoxicity is in those patients who were also receiving other drugs for, let's say, cancer therapies.

For example, on slide CS-14 and CS-16, the CS-14 patients were only in TGCT patients, and all of those patients recovered. Of course, this is still a limited dataset. Of course, it's not as longitudinal as we would like, but all of those patients recovered.

Am I reading that correctly as compared to CS-16, where those patients were also receiving cancer therapy and had adverse outcomes -- well, had non-recoverable outcomes?

DR. RINI: I think so. Yes, I think you're reading that correctly.

Any other discussion items? Okay; one more.

DR. VILLALOBOS: Quickly on REMS component. I understand that it's necessary to follow up for data and see if there's long-term effects of this. However, it also is an onerous activity. Will that unnecessarily reduce access to this drug to patients that actually need it?

Understandably, these are primarily being given by oncologists who give drugs that are typically much more toxic than this drug. So understanding that this is a benign disease, though with significant morbidity on its own, is this absolutely necessary to include a REMS overall for this drug?

DR. FASHOYIN-AJE: The is Lola Fashoyin-Aje from the FDA. I think your points are well taken. I think we have some proposals on the table that are under discussion to minimize the burden of the REMS, and we recognize it very well. Many of us are medical oncologists and have had to train to be certified.

However, I think that the issue of this disease not being a lethal one is one that is I think critical to understanding why if approved, FDA would be requiring a REMS. I think as Dr. Strader mentioned, the liver injury that we've seen and the liver injury that may be occurring that we have not observed clinically or that is maybe subclinical, we have some hint of that from

the few biopsies that were obtained, really require that prescribers be well informed as to the risk of hepatotoxicity and the appropriate patient population for whom this would be an appropriate therapy.

So we feel strongly that if approved, a REMS would be required, even with considering the burden of such a program.

DR. VILLALOBOS: That was Victor Villalobos, UC Denver.

DR. RINI: Thank you.

If there's no further discussion on this question, we'll now begin the voting process. We will be using an electronic voting system for this meeting. Once we begin, the vote buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the

vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. Please also state the reason why you voted as you did, if you'd like to.

I'm going to go back and basically just summarize the discussion. I think what we heard was that I think most people believe there's benefit to this drug, certainly as evidenced by response rate. I think there's less certainty around the PRO type data with all the missing data and just whether or not that's meaningful to patients. There's no question it's meaningful to individual patients as we heard here today and saw the more dramatic anecdotes and the context of the benefit and the absolute benefit on a grand scale.

I think the other major theme around the discussion was regarding hepatotoxicity and the REMS, in that there's concern over hepatotoxicity and certainly that a REMS is needed to monitor, and

that there are still a lot of open questions given the relatively small sample size because of the rarity of the disease around drug and dose and duration and context, and all that in terms of a risk of hepatotoxicity.

This is the question that we'll be voting on. Does the demonstrated benefit of pexidartinib outweigh the risk of the drug in the proposed indication? Are there any questions regarding the actual voting question?

(No response.)

DR. RINI: Please press the button on your microphone that corresponds to the vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or wish to change your vote, please press the corresponding button again before the vote is closed. Please vote now.

(Voting.)

LCDR SHEPHERD: For the record, the vote is 12 yes; 3 no; zero abstain; and zero no voting.

DR. RINI: Now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, please state the reason why you voted as we did into the record.

P.K. is not voting. Do you want to comment on anything?

(Dr. Morrow gestures no.)

DR. RINI: No. Okay. Starting with Dr Calis, your vote and the reason why you voted as you did.

DR. CALIS: I voted yes, and the reason for that is simply that I believe the data regarding the efficacy in the context of a debilitating condition. I am very concerned about the liver toxicity. I'm supportive of the REMS. And I think that it would be helpful, but I'm also concerned about the liver injury, the direct liver injury and how much -- I think more of the REMS is going to be weighted towards evaluation than mitigation maybe possibly. But hopefully it will be used in the context of a restricted system so there can be

adequate monitoring. But I'm still concerned about those patients that may have this unpredictable liver toxicity.

DR. VILLALOBOS: Victor Villalobos. I voted yes. This is an ultra rare disease with no good therapies available to patients for it and that it can be highly morbid. I feel that getting more real-world data on how we can use this drug in a safe and effective manner will be really important for the academic community going forward.

DR. LEWIS: Val Lewis, MD Anderson. I voted yes. While I'm quite concerned about the ramifications of the drug on the liver, this drug does have the potential really to be life changing for those individuals who have the diffuse PVNS.

DR. STRADER: Doris Strader. I voted no. While I am very sympathetic to the fact that this drug causes some debilitating effects for people that can be lifelong, I was concerned about the missing data and was not convinced that there was real clinically meaningful benefit.

Likewise, while I understand that the

hepatic injury is not liver failure, I am concerned that this may be persistent for a lifetime, and I worry that there was not enough to suggest that there was going to be rigorous monitoring of patients over their lifetimes.

DR. WEINFURT: Kevin Weinfurt. I voted yes. My vote was informed by the considerations raised earlier, this being a rare condition for which there are no good options. It seems pretty clear that there's a signal here. It's frustrating to not be able to characterize the exact distribution of benefit in this case, but it seems to me sufficient enough to start to get more experience with it with careful monitoring.

MS. BROYLES: Susan Broyles, patient rep, and I voted yes because of the clinical benefit that is apparent in the patients that are here plus the study results. The hepatic problem needs intense follow-up certainly, but I think the patients that face this have had no other recourse, and this at least opens up some doors for them. Thank you.

MS. PREUSSE: Courtney Preusse, consumer rep. I also voted yes for the reasons already stated, as well as what somebody mentioned earlier, which is by doing nothing, there's injury of the disease itself, potential amputation, the loss of mobility. There are effects and a lack of treatment options for patients living with the disease.

It's not like doing nothing means that these patients will continue on indefinitely with mobility. It's quite the opposite. So this provides patients with an option to at least try to continue some normal semblance of life. Thanks.

DR. HOFFMAN: Philip Hoffman. I voted yes. While I do take Dr. Lewis' comment earlier about this is a minority of a minority that responds to this, I think it's basically an orphan drug. It's a rare condition, and it's the only thing that is available when surgery is no longer an option.

I am heartened by the fact that because this is only going to be available through specialty pharmacies, and registered physicians, and the REMS

program, I am comfortable that the liver risk is going to hopefully caught early and monitored. And it may turn out, as has happened with REMS in other drug approvals, that eventually it may even disappear if we find out that it's easier to manage than we think it is.

DR. KLEPIN: Heidi Klepin. I voted yes for many of the reasons that were articulated. This is an unmet need. It's a very debilitating disease. There's evidence of efficacy, and I found the PRO evidence to be supportive despite the limitations.

Like others, like everyone, I think, I'm concerned about the hepatotoxicity. I was somewhat reassured by the data supporting the reversibility for the patients on this trial as opposed to some of the other data that was pointed out, and also the fact that there is a plan for monitoring. I would just echo others in saying I think the REMS program will be important. I'm reassured by the fact that it might be a little bit more difficult to prescribe it, so I think that's actually going to be important initially, to make sure the right

people are actually doing the prescribing, that they're educated, they know what to do.

I'm reassured that there will be a registry and echo the sentiment that it needs to hopefully persist long enough to give us some data past that 2-year mark so that we can really understand late effects; and then would echo the importance of education, not just for providers but for patients as they're interfacing with their other providers so that they have some information to be able to take to their primary care doctor just to make sure everybody's in the loop about here's something I'm taking, here are the things we need to be thinking about, and then making sure that for providers, that we are disseminating ongoing results so that we can further refine our discussions with patients.

DR. RINI: Thank you. Brian Rini. I'll go last so I can summarize. Greg?

DR. NOWAKOWSKI: Greg Nowakowski. I voted yes, primarily because it's an active drug in this indication, which results in significant response

rates and hopefully will translate to clinical benefit.

I am concerned about liver toxicity. Like the others, I think the REMS program, which is in place, will alleviate some of these concerns, in addition to patient selection for the therapy will be very important. I think the orthopedic surgeon colleagues agreed that this is a drug for a minority of the minority patients, so if you actually select the right patient population, those which are really in a very dire situation, this could be a benefit and work this benefit-to-risk ratio even with this risk of liver toxicity.

DR. ULDRICK: Tom Uldrick. I voted yes as well. I think that the activity data was quite compelling, and really the hard part in a study like this is showing the clinical benefit. I think the totality of the data that was shown suggests that there probably is clinical benefit. There are intrinsic problems with the range of motion as an endpoint.

I was perhaps most swayed by the PROMIS

tipping-point analysis. PROMIS is a tool that's been used in other rheumatologic diseases, and the degree of benefit that was shown in the sensitivity analyses appears to be what's been accepted as presented by the sponsor and other diseases like rheumatoid arthritis.

So when I look at a drug that has a response rate of about 50 percent, as you look in people who stay on it, and a range of qualities that suggest clinical benefit, I think that that benefit of 0.3 percent severe liver toxicity ratio is acceptable, especially if and when you have a REMS program.

DR. CRISTOFANILLI: Massimo Cristofanilli, and I voted no because the question was very clear; if there is any doubt that there is a risk benefit for this drug if it gets approved? I think many questions have been raised.

First of all, the clinical trial, a small trial with a lot of missing data. If this was an incredible condition, we will probably discuss the same issue. The patients also had signals of significant liver toxicity I think we were all

raised [indiscernible] about. The disease itself is not a terminal condition. It's certainly debilitating, and there is an alternative that surgery, in some point, when you get to an advanced disease, is just not possible.

The other thing is that the label indication suggests to me if this drug goes out in the community, it will be used in place of surgery for patients who are simply symptomatic because being inoperable is a very subjective criteria. These are the reasons for which I voted no.

DR. HALABI: Susan Halabi. I also voted no. While I do recognize there is an unmet need and this is a rare disease, in my opinion, looking at the data, while there is some clear activity for the drug, I was concerned with exposing the patients to hepatotoxicity.

I was also concerned about the clinical outcome data because a lot of the problems [indiscernible] and other quality-of-life data were based on unvalidated scales, with the exception of PROMIS. There were a lot of missing data, although

the sensitivity analysis did show it's going in the right direction.

The final concern I had, I did not see longitudinal data beyond the 25 weeks, and that's why I took more of the conservative side because I was worried about the efficacy and quality-of-life data beyond 25 weeks.

DR. HUNSBERGER: Sally Hunsberger. I took the other view. I believe the sensitivity analyses do show that there is an effect. We can't quantify the effect. I thought the primary endpoint of tumor shrinkage was very strong, so I thought that was important.

I think the REMS program will be really important, and that's our best way to get safety data and understand the long-term effect. I think also what's going to happen in practice is what we saw happen in the study, which is that if you have progression or if you have severe adverse events, people are going to stop using the drug. So it's not like they're going to go on it and stay on it, even if there's no benefit.

So I think the study actually showed us what's going to happen in real life, but I do think the REMS program will be really important.

DR. RINI: Thank you. Brian Rini. Just to summarize, I voted yes. I think what we heard is that the strengths are this is a clearly -- although rare, morbid, and debilitating condition without any viable systemic options. I think the response rate was robust as I think everybody mentioned. I think there is a belief in the functional improvement even despite some of the limitations of the data. I think somebody over here said it, that I think certainly for individual patients this has the potential to be a life-changing drug.

I think some of the weaknesses are as mentioned, just the limitations of the functional analysis in the missing data. I think the hepatotoxicity is clearly a concern, especially, as I think Heidi mentioned, in young patients, the education. I have young germ-cell patients, and they tend to get lost to follow-up, and they don't

want to get their LFTs checked twice a week. So I think patient education and provider education in the REMS will be critical.

I think there are still a lot of questions about how best to administer the drug, in whom relative to timing of surgeries, how long the dose, and duration. We heard a number of questions that will need to be sorted out moving forward, but in summary, I think there was a positive benefit-risk to the drug.

Adjournment

DR. RINI: We'll now adjourn the morning session and break for lunch. We'll reconvene in this room at 1:00, at which time we'll begin the afternoon session. Thank you.

(Whereupon, at 11:50 a.m., the morning session was adjourned.)