FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Wednesday, March 29, 2017

8:00 a.m. to 10:53 a.m.

Sheraton College Park North Hotel

Chesapeake Ballroom

4095 Powder Mill Road

Beltsville, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. ROTH: Good morning. Welcome to the March 29th ODAC meeting. I'd like to first remind everyone to please silence your cell phones or any other device that makes noise, if you've not already done so. I'd also like to identify the FDA press contact, Angela Stark. Angela is standing in the back of the room on the left, for any press issues.

I'm going to go around the table. We have a couple new members and have everyone identify themselves, if you'd just push the talk button on your microphone, identify yourself to be read into the record. Thanks.

DR. MORROW: Phuong Khanh, PK Morrow, industry representative.

DR. WALDMAN: Scott Waldman, clinical pharmacology, Thomas Jefferson University in Philadelphia.

DR. KARARA: Adel Karara, University of Maryland Eastern Shore.

MR. MAJKOW SKI: Paul Majkowski, Uniondale, New York, patient representative.

DR. SHAW: Alice Shaw, medical oncology, Massachusetts General Hospital in Boston.

DR. COLE: Bernard Cole, biostatistics, University of Vermont.

DR. ROTH: Bruce Roth. I'm a medical oncologist from Washington University in St. Louis and chair of the committee.

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

DR. ULDRICK: Thomas Uldrick, medical oncologist, Center for Cancer Research, NIH.

DR. KLEPIN: Heidi Klepin, geriatric oncology, Wake Forest.

DR. BURSTEIN: Hal Burstein, medical oncologist at Dana-Farber Cancer Institute in Boston.

DR. OKUSANYA: Olanrewaju Okusanya, clinical pharmacology reviewer, FDA.

DR. YE: Jingjing Ye, statistic reviewer at FDA.

DR. SCHWARSIN: Alexandria Schwarsin, clinical reviewer at the FDA.

DR. DE CLARO: Angelo de Claro, clinical team leader, FDA.

DR. PAZDUR: Richard Pazdur, director, OCE, FDA.

DR. ROTH: Go ahead.

MS. PREUSSE: So sorry I'm late. Courtney Preusse, Fred Hutch, Seattle, Washington, patient advocate.

DR. ROTH: Thank you, and welcome to committee.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the

record only if recognized by the chairperson. We look forward to a productive meeting.

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

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I'll pass it on to Dr. Lauren Tesh, our DFO for this meeting, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. TESH: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee meeting 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 discussion 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 the purposes of 18 U.S.C., Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves biologics license application, BLA 761064, rituximab/hyaluronidase injection for subcutaneous use, submitted by Genentech, Inc.

The proposed indication/uses for the product

are for the treatment of patients with relapsed or refractory, follicular lymphoma as a single agent; previously untreated follicular lymphoma in combination with first-line chemotherapy and in patients achieving a complete or partial response to rituximab/hyaluronidase for subcutaneous injection in combination with chemotherapy; as a single agent maintenance therapy; non-progressing including stable disease follicular lymphoma as a single agent after first-line cyclophosphamide, vincristine, and prednisone chemotherapy; the treatment of patients with previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisolone or anthracycline-based chemotherapy regimens; and in combination with fludarabine and cyclophosphamide for the treatment of patients with previously untreated and previously treated chronic lymphocytic leukemia.

This is a particular matters meeting during which specific matters related to Genentech's BLA 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 the FDA's invited industry representative, we would like to disclose that Dr. P. K. Morrow is participating in this meeting as a non-voting 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. ROTH: Thank you, Lauren.

We'll begin with FDA remarks, and we'll start with Dr. Angelo de Claro presenting for the agency.

FDA Opening Remarks – R. Angelo de Claro

DR. DE CLARO: We are here today to discuss an application for a rituximab and hyaluronidase product for use as an injection for subcutaneous use. We will refer to this product as rituximab SC or rituximab subQ.

The rituximab subQ product is distinct from the rituximab product for intravenous use, Rituxan. Intravenous rituximab received initial approval in 1997 and is approved for oncologic and rheumatologic indications in the U.S. The rheumatology indications include rheumatoid arthritis, granulomatosis with polyangiitis, also

known as Wegener's granulomatosis, and microscopic polyangiitis.

The rituximab subQ application seeks the following indications in oncology, which are consistent with approved oncologic indications for intravenous rituximab. The wording of the proposed indication is shown in the next two slides. These indications include follicular lymphoma for the three settings noted in the slide, and for diffuse large B-cell lymphoma, and chronic lymphocytic leukemia.

Comparison between the rituximab IV and rituximab subQ products is shown in this table. Patients to be treated with rituximab subQ must receive at least one full dose of intravenous rituximab. The administration information described in the table is for the follow-up doses.

The follow-up dose for IV infusion is given over 1-and-a-half to 2-and-a-half hours while the subQ product allows for administration over approximately 5 minutes. Other notable differences include the increased concentration of rituximab in

the subQ product to allow for delivery volumes between 11 to 13 mL and co-formulation with hyaluronidase.

Hyaluronidase is approved in the U.S. as a standalone product to facilitate the absorption of injected drugs. Rituximab IV dosing is based on body surface area. While the proposed dosing for rituximab subQ used as fixed, which is also termed as a flat-dosing regimen.

The 1400-milligram subQ dose was compared to the 375-milligram per meter squared IV dose, and the 1600-milligram subQ dose was compared to the 500-milligram per meter squared IV dose.

The rituximab subQ product was submitted for regular approval as a 351(a) biologic as defined in the Public Health Service Act. The biologic must be shown to be safe, pure, and potent, to be approved. The concept of potency has long been interpreted to include effectiveness.

This product is not a biosimilar, which is important to know because the approval requirements for biosimilars differ. 351(a) biologic

applications require the conduct of adequate and well-controlled clinical trials to support the proposed indications.

As noted in the 1998 FDA guidance on effectiveness, in certain cases, effectiveness of an approved drug product for a new indication or effectiveness of a new product may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen, or dosage form.

The guidance also stated that it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic PK data without an additional clinical efficacy trial. In general, pharmacokinetic data refers to analyses of drug concentrations in the human body. Most often, these analyses focus on drug concentrations in the plasma.

This application uses a PK bridging approach to establish the safety and effectiveness of the rituximab subQ product. FDA has used PK bridging approaches to support new routes of administration for approved drugs. Examples were provided in page 10 of the FDA briefing book.

A notable feature in this application was the use of a PK bridging approach that targeted a trough concentration for the rituximab subQ product that would be at least as high as that achieved with IV rituximab. Additional changes include the use of a fixed-dose regimen and the use of hyaluronidase to facilitate drug absorption.

FDA requests discussion at this meeting for the advisory committee to provide feedback and insights on the development approach and assess whether the results of the clinical trials support the approval of the rituximab subQ product for the proposed indications in follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia. Thank you.

DR. ROTH: Thank you, Dr. de Claro.

We'll now move on to the applicant presentation.

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

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

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

of your presentation, it will not preclude you from speaking.

We'll now proceed with the applicant presentations.

Sorry, Arthur, if you could read your name into the record.

DR. HARRALSON: Yes. My name's Art Harralson. I'm an associate dean at Shenandoah and George Washington University.

DR. FARRELL: My name is Ann Farrell. I'm the division director of the Division of Hematology Products.

DR. ROTH: Thanks, Ann.

Okay. You can go ahead. Thank you.

Applicant Presentation – Nancy Valente

DR. VALENTE: Good morning, Dr. Roth, committee members, FDA representatives and guests. My name is Nancy Valente, and I'm the head of hematology development. I'm trained as a hematologist and oncologist.

I've had the privilege of being involved with the development of rituximab over the last 13

years and witnessing the transformative benefit this has brought to patients with hematologic malignancies like lymphoma and CLL, and I'm really pleased to be here today to share with you and introduce you to rituximab subcutaneous, a new therapy that was designed to improve the patient experience while maintaining the established benefit-risk profile of rituximab.

I hope to share with you the development rationale for rituximab subcutaneous, convey that this is the same rituximab antibody we all know, and describe our development approach.

Rituximab subcutaneous is a simpler, faster way to deliver the benefit of rituximab. It dramatically shortens the administration time from hours to 5 to 7 minutes, and this is the time that the patient would spend in clinic.

It's a ready-to-use, fixed dose, as compared to the BSA adjusted dosing of rituximab IV, and it's very simple to administer. Using a syringe and a needle, the product's withdrawn from a single-use file and injected under the skin. So

the treatment burden is not only decreased for the patient, but also for the healthcare provider, such as the pharmacist and the nurse. For physician practices that are at capacity, it has the opportunity to improve access for this important therapy.

In our program, as Dr. de Claro mentioned, the first infusion remains intravenous, but all subsequent infusions are delivered by the subcutaneous route. And as you'll hear later, the patients actually prefer this route of injection.

You may be wondering what the differences are with rituximab IV. Importantly, this contains the same rituximab antibody that's widely used and approved, and we found as we attempted to concentrate the rituximab, that at its maximal concentration, we were still left with a volume of approximately 11 to 13 mLs, which is larger than a typical subcutaneous injection.

We found a novel approach to address this, and that was with the combination with hyaluronidase, which facilitates this volume of

injection. Both of these products are previously approved. Extensive product testing has demonstrated that's there's no impact on the rituximab on its activity or its stability.

Human hyaluronidase has been well-characterized, and I'm going to share some of these characteristics with you. So recombinant human hyaluronidase is a permeation enhancer. It depolymerizes hyaluronan found in the subcutaneous space, which is natural barrier to fluid dispersion. So this allows for the rituximab to be dispersed.

It's local, reactive, very rapid and transient, with a very short half-life. It decreases swelling and induration, and they hyaluronan within the subcutaneous space is restored very quickly, within 24 to 48 hours. There's only a small amount of hyaluronidase within this product, and it can't be systemically detected. It doesn't circulate.

Recombinant human hyaluronidase was approved in 2005 for the dispersion and absorption of other

injected drugs, and doses have been given to more than one million people.

I'll now move to our regulatory framework. Our development program was based on and informed by principles of FDA guidance for a change in formulation of an established product like rituximab IV. We expanded this and went beyond the requirements to conduct a very comprehensive and broad development program so that we could evaluate the efficacy, safety, and patient preference.

Using this framework, we developed a PK clinical bridging approach for our development program. We had three clear objectives when comparing the subcutaneous to the IV formulation. The first was to establish non-inferior exposure of rituximab. The second was to establish the comparability of safety and effectiveness of the subcutaneous to the IV formulation. And the third was to evaluate the patient preference or satisfaction with the route of injection.

This table describes our broad development program. You can see that more than 2200 patients

were enrolled and greater than 1500 were treated with rituximab subcutaneous. There are five unique studies. These were conducted in patients with follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia. They include the evaluation both as a monotherapy and in combination with standard of care chemotherapy.

The checkmarks identify how each of the studies addressed the PK clinical bridging program, the important components of that program, including PK, efficacy, safety, as well as patient preference. The patients enrolled in these studies are typical lymphoma and CLL patients that you would treat in clinic, and they're very similar to the patients that were enrolled in studies that led to the approval of rituximab IV.

Those studies I just showed you comprise our integrated or interlinked clinical development plan. You can see NHL and CLL are described separately, and that's because rituximab IV has established doses and schedules for each of those that are unique.

The program began with dose finding with a goal of determining the rituximab subcutaneous dose that would provide a non-inferior exposure to rituximab IV at the established dose and schedule. We then confirmed that. The program was then expanded to evaluate safety, efficacy, and importantly, patient preference for the route of injection.

In this program, we went from the BSA adjusted dosing of rituximab IV to fixed dosing, which supports our overall goal of decreasing the treatment burden, as well as subcutaneous administration. You'll hear more about the program in the subsequent presentations by Dr. Boehnke and Dr. Morcos.

We are seeking the full approval for the oncology indications that have been approved for rituximab IV. This includes the treatment of follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia.

We are confident that the data that you will see today will demonstrate that we have achieved

our goals of decreasing the treatment burden for patients, improving their experience, while maintaining the established risk benefit profile for rituximab.

Our presenters today include Dr. Andrew Davies, a lymphoma expert who will describe the clinical perspective. He's also the principal investigator for the SABRINA study for follicular lymphoma.

He will be followed by Dr. Peter Morcos, our pharmacologist, who will describe the PK clinical bridging approach and PK data. Dr. Boehnke will describe the clinical efficacy, safety, and patient preference data, and provide concluding remarks.

We are also joined by two distinguished consultants. Dr. John Gerecitano is a lymphoma expert and the head of a large outpatient infusion center for the treatment of lymphoma at Memorial Sloan Kettering Cancer Center. Dr. Donald Mager is a professor of pharmacology and an expert in the pharmacology of antibodies. They are both available for questions.

I will now ask Dr. Davies to provide his clinical perspective. Thank you.

Applicant Presentation - Andrew Davies

DR. DAVIES: Thank you very much, Dr. Valente.

My name is Andrew Davies. I am a medical oncologist from the University of Southampton in the United Kingdom, and I am the global principal investigator on the SABRINA study, which we are going to discuss the data today.

In Europe, the UK, and many other territories, the introduction of administration of rituximab by the subcutaneous route has had a really significant impact upon burden of care for patients. The change in delivery of rituximab has made a difference significantly from a day-case infusion to something that can be delivered in the patient's lunchtime. I hope that I'm able to share some of that experience that we've gained in Europe with you today.

So I'd like to first of all declare that I do conflicts of interest. I'm a person who does a

lot of novel drug development, but specifically I have received research funding and travel expenses, along with honoraria from Roche-Genentech.

I'd like to just give a little bit of context about the non-Hodgkin's lymphomas and CLL, a little bit of context about what a significant difference rituximab has made in the light of patients with non-Hodgkin's lymphoma and CLL, and then talk a little bit more about the delivery of the subcutaneous formulation.

There are 72,000 new cases of non-Hodgkin's lymphoma each year in the U.S., and there are almost 600,000 patients living with the disease. CLL has an instance of about 19,000 patients every year, and again a burden of about 120,000 people living with the disease in the U.S.

The most common of the B-cell malignancies are diffuse large B-cell lymphoma and follicular lymphoma. Now both follicular lymphoma and CLL are incurable with conventional therapies, and patients have a chronic relapsing and remitting course, and often over a lifetime experience numbers of lines

of therapy, so repeated lines of treatment. And those are primarily chemotherapy, but in combination with the anti-CD20 monoclonal antibody, rituximab. So we have multiple lines of therapy over a lifetime.

So rituximab, the IV formulation, has been approved since 1997, and almost 4.5 million patients have been treated with rituximab. It's completely embedded in the standard of care for our patients, and that's reflected in the NCCN guidelines, and it's reflected in multiple international guidelines.

We've got 20 years of experience using rituximab. It's well-characterized at depleting B cells, and we could clearly -- in many diseases, it prolongs progression-free survival and overall survival. Importantly, we have a well-established safety and efficacy profile, and it's listed as an essential medicine by the World Health Organization.

I just really want to give you a little bit of a flavor about what the impact of rituximab has

been in these various diseases. In diffuse large B-cell lymphoma, there's no doubt it's changed the clinical course of the disease. In the first randomized study between conventional CHOP chemotherapy and the rituximab and CHOP chemotherapy, delivered by the French GELA group, at 10 years follow-up, there's an increase in overall survival by 16 percent through the addition of rituximab to chemotherapy. In a population-based series from British Columbia, we also see the same.

So we see a clear improvement in outcomes in a whole population, rather than just a confined clinical trial population with the addition of rituximab. So rituximab has changed the face of diffuse large B-cell lymphoma.

In follicular lymphoma, we see that it improves response rates. It improves event-free survival when just used with induction chemotherapy. Here's an example with CDP. But we also use rituximab in the maintenance setting, and we deliver this every 8 weeks in first remission,

and that's associated with a clear improvement in progression-free survival with a hazard ratio of 0.5.

The bottom curve shows data from the SWOG group that show that the sequential addition of improved chemotherapies and more latterly with the introduction of rituximab has improved overall survival in this disease.

In CLL, we know that the addition of rituximab to fludarabine and cyclophosphamide chemotherapy clearly improved progression-free survival, and this is an impressive curve taken at six years of follow-up from the CLL8 study.

So there are of course problems with delivery of the IV formulation. It takes time to deliver. Even at the most rapid rate, it takes us 90 minutes, and can take 4 hours to deliver. The patient needs to be prepared, needs to be cannulated. During the infusion, they need to have serial vital sign measurements and observations.

It's based intravenously on a body surface area. So for each patient, dose needs to be

calculated at appropriate dilution. The final administration volume is required in the pharmacy. And if you think about giving this over multiple treatments -- for example, I've mentioned you may have something like 4 months worth of induction followed by 2 years of maintenance, this is multiple cannulations over a 2-and-a-half year period. And again, with sequential treatments, this is multiple cannulations over a lifetime.

So the subcutaneous route is a fixed dosing for all patients. It comes in a ready-to-use vial delivering an injection volume of 11 to 13 mLs and is given over 5 to 6 minutes. And that contrasts with the body surface area calculated dose, the preparation, the IV bag formulation, et cetera.

So the patients, it takes about 6 minutes to deliver. It's very comfortable. We get the patient to sit in a chair, and often we get the patient to hold a stopwatch so that they know how long the infusion time takes. And it's really good contact time with the nursing staff and the patient during that 6-minutes infusion.

So subcutaneous rituximab offers really meaningful clinical benefits. It builds on the depth of experience of rituximab IV over 20 years and really does improve the patient experience. It offers a simpler, faster, and less invasive treatment and a great experience. It reduces the amount of time for patients that spend in the clinic. And as I say, we've changed this from being a whole day infusion to being something that's delivered in the patient's lunchtime.

Patients prefer the subcutaneous route. And for somebody who runs a busy chemotherapy service, there is no doubt that this change in administration time has had a significant impact on our burden and has freed up significant capacity in our day wards. Thank you.

Applicant Presentation - Peter Morcos

DR. MORCOS: Thanks, Dr. Davies, for that clinical perspective.

Good morning. My name is Peter Morcos. I am the clinical pharmacologist for rituximab subQ, and today I'll be discussing the clinical

pharmacology concepts and components of the rituximab subQ clinical development program.

You've seen this slide before. The rituximab subQ clinical development program sought to achieve three main objectives. I'll be discussing the first key objective, which was to establish non-inferior exposure as part of the innovative PK based clinical bridging approach.

Over the next few slides, I will introduce the rituximab PK based clinical bridging, the scientific considerations which went into designing the program, and the key clinical pharmacology outcomes from the dedicated studies.

So as introduced by Dr. Valente in the introduction, PK bridging was used to establish rituximab subQ, as in fact, we're administering the same monoclonal antibody in both formulations. The rituximab subQ PK bridging was designed based on our knowledge or rituximab's mechanism of action and the clinical experience we've gained with rituximab over the course of its use.

We know that rituximab exerts its

anti-B-cell action upon binding to its target, CD20, on the surface of malignant B-cells, eliminating these cells over time. This is visualized in the cartoon on the right.

The scientific consideration was met by ensuring C-trough levels or the lowest concentrations of rituximab, or at least as high with rituximab subQ as they are with the established IV dosing regimen, then we should expect similar target occupancy. Therefore, then we should expect the same anti-B-cell activity. It should be achieved regardless of route of administration. And indeed, if we examine the clinical experience we've gained with rituximab IV, we can see there is an association between C-trough and rituximab's anti-B-cell clinical response.

What I illustrate here, and what I apologize is a very busy slide, are the pharmacokinetics and B-cell time course profiles in patients who responded and did not respond in the early studies of rituximab IV given as monotherapy.

What we see first in the responder patients

in the PK profiles is that if you look in the circled area, we see the C-trough values for these responders are consistently high and stable, and you see overall low PK variability as you see nice, tight lines together. The resulting B-cell profiles on the bottom left illustrate a good depletion of B-cells in these patients.

Conversely, if you look on the right side of the figure, we see in non-responding patients C-trough values which are quite low and sporadic, and with associated high PK variability, you see a large spread in the data. The resulting B-cell profiles on the bottom right in these non-responders clearly illustrate poor control of B-cells.

This early experience from the rituximab IV program helps illustrate the association between rituximab C-trough and some of the clinical outcomes. And indeed, some follow-on multivariate analyses supported this association between C-trough and anti-tumor or anti-B-cell effect.

In determination of the most clinically

relevant exposure endpoints for bridging between the two routes of administration, we considered C-trough as the most appropriate primary PK endpoint, as again it considers the mode of action of rituximab and has shown to be associated with clinical outcomes. Of note, this has been supported by other independent investigations and relationships between rituximab exposure and outcomes.

AUC or area under the curve, another PK parameter which is often estimated from data, provides important information on the exposure of rituximab over the course of a treatment cycle, and this could potentially also contribute to the anti-B-cell action of rituximab. So AUC was considered a key secondary endpoint as part of our investigations.

On the other hand, Cmax, or P concentrations, was not considered an appropriate parameter to bridge between these two routes of administration. Notably, Cmax following IV infusion, which is the currently approved dosing

route for rituximab, mainly reflects the end of infusion concentration in which the entire dose is deposited directly in the systematic circulation, and doesn't reflect the distribution of rituximab to B-cells or to other sites of action.

It's not also been shown to be clearly correlated with outcomes. So based on this, we focused on C-trough and AUC as part of our PK based clinical bridging.

With this concept in mind, I'll now move into the clinical development program for rituximab subQ primarily around the PK based clinical bridging.

Again, you've seen this slide in the introduction. The rituximab subQ clinical development program was an integrated approach, which investigated, really, dose-finding, dose-confirmation, and clinical outcomes. I'll now focus on the dose finding and dose confirmation aspects through the clinical development program.

As part of the integrated clinical development for rituximab subQ, dedicated

dose-finding studies were undertaken to investigate rituximab subQ doses to identify the most appropriate doses, which correspond to the approved IV dosing regimens in the NHL population, as well as the CLL population.

The first in human trial was the SparkThera stage 1 illustrated at the top of the screen, in which single subcutaneous doses of rituximab were administered to patients to characterize its PK and to support identification of an appropriate dosing regimen, which corresponds to the approved IV dosing regimen for rituximab.

The intensive PK collected from this study was integrated into an established population PK model, which was built on the extensive experience we've gained with rituximab IV, and this was used to identify a fixed subcutaneous dose, which most appropriately correspond to the approved IV dosing regimen.

As Dr. Valente mentioned, we focused on identifying fixed subQ doses in an effort to facilitate drug preparation, and in the spirit of

reducing the overall treatment burden for patients.

Those data also help support a starting dose to investigate in the CLL population, and a second dedicated dose-finding study was undertaken in the CLL population in SAWYER stage 1 at the bottom of the screen to investigate further subcutaneous doses and to characterize the PK and the CLL population.

Data from these studies were again integrated into the established PK model for rituximab, and again, fixed subcutaneous doses were identified to most appropriately correspond to the approved IV dosing regimen in the CLL population.

Results from those analyses indicated that a dose of 1400 milligrams in the NHL population and a dose of 1600 milligrams in the CLL population would be the most appropriate subcutaneous dose, which corresponds to the approved IV dosing regimens in these two patient populations.

Once doses were selected, we then moved into our dose confirmation studies in which three independent trials powered for non-inferiority of

C-trough investigated the ability of the fixed subcutaneous doses, which were selected to in fact demonstrate non-inferiority of exposure relative to the established IV dosing regimens.

Namely, the three studies investigated, the clinical established dosing intervals and dosing schedules of rituximab, the every 2-month and every 3-month dosing interval in the NHL maintenance population in SparkThera stage 2 at the top, the every 3-week dosing in NHL induction in SABRINA stage 1 in the middle, and the every 4-week dosing in the CLL population in SAWYER stage 2.

As you can see, each of these studies were head-to-head trials, which investigated the selected rituximab subQ doses against the established IV dosing regimens.

As I mentioned, the primary endpoint was C-trough in demonstration of non-inferiority. And we focused on demonstrating non-inferiority as we wanted to ensure that the fixed subQ doses do not lead to any risk of under exposure in this patient population.

Results from those dose confirmation studies are illustrated on the screen, for the primary PK endpoint C-trough on the left side and the key secondary endpoint AUC on the right side. What you're seeing in these visuals are the geometric mean ratios, or the ratio of subcutaneous to IV for the respective PK parameter, and the associated 90 percent confidence interval for those PK parameters.

What you can see for both the primary and the secondary PK endpoints is that across all the clinically established dosing intervals, which have been investigated in those independent trials, confirm non-inferiority of rituximab subQ relative to the IV.

The lower bound of the respective 90 percent confidence intervals exceed the prespecified boundary of 0.8 across all clinically established dosing intervals, across populations, and across the primary and secondary PK endpoints. Therefore, these three independent trials for dose confirmation meet their primary endpoints in

establishing rituximab subQ is non-inferior to that of rituximab IV.

As I've mentioned, we focused our efforts to identify fixed subcutaneous doses in an effort to reduce treatment burden on patients. So as you move from a BSA base to a fixed dose, there could potentially be a change in the distribution of overall exposures with potentially going to a fixed dose, a potentially lower exposure and heavier or high BSA patients, and potentially a slightly higher exposure in smaller, lighter, or low BSA patients.

So it's important to ensure that the fixed subcutaneous doses not only achieve non-inferior exposure in the overall population, but also within patient subgroups.

Results on this slide illustrate the distribution of exposures achieved following the fixed subcutaneous doses in the NHL population and the CLL population for the low, medium, and high body surface area categories for the fixed subcutaneous dose, relative to the established IV

dosing regimen.

As you can see, the fixed subcutaneous dose in both the NHL and the CLL population achieved non-inferior exposures across the entire body surface area range, including in the high BSA group who are at potential risk for underexposure. Therefore, these fixed subcutaneous doses demonstrate non-inferiority across the entire BSA range.

In consideration of any potential exposure differences, which may arise due to the fixed subcutaneous dose, we've also investigated the relationship between rituximab subQ exposures and clinical outcomes, namely clinical safety outcomes.

You see on this slide, again the NHL on the left and the CLL population on the right, is the distribution of exposures following rituximab subQ administration for patients reported at various grades of safety events, including those who did not report a safety event, or a grade of safety event, and those were reported, those various grades.

As you can see, the baseline distributions of exposures, no clear, no apparent correlation is observed between rituximab exposure and clinical safety outcomes. These analyses help support that exposure differences, which may arise following subcutaneous administration, are not expected to result in any increased risk of safety events.

Finally, if we consider the scientific considerations, which went into designing the PK bridging program that I started with at the beginning of this presentation, we indicated we've given the same monoclonal antibody just via two different formulations, and that by using PK bridging, we can establish rituximab subcutaneous.

We identified the most clinically relevant PK endpoints to investigate as part of PK bridging, and we demonstrated that those PK endpoints achieved their non-inferior exposures in three independent trials.

Getting back to the scientific considerations, we also then indicated that if we achieve exposures following subQ, at least as high

as those following the established IV dosing regimen, then we should expect the same mechanistic effect with rituximab and really the same anti-B-cell action regardless of route of administration.

So the results from these dose confirmation studies establish PK bridging for the subcutaneous route, but we've also extended this to investigate the effect of administering these two routes of administration on rituximab's anti-B-cell action.

Results are illustrated here for those pharmacodynamic results, and what you see on the left and right side in the NHL and the CLL population are the effect of rituximab on B-cells. So these are the B-cell time courses following administration of rituximab IV and the rituximab subcutaneous doses.

What you can see from these figures is highly consistent and super-imposable profiles of rituximab B-cell depletion, maintenance of B-cell depletion, as well as repletion kinetics when you withdraw rituximab treatment, following either IV

or the subcutaneous dose. So not only is the PK bridging established, but also this is extended to demonstrate highly consist pharmacodynamic results as well.

In summary, PK bridging has been used and has confirmed fixed subcutaneous doses, which correspond to the established and approved IV dosing regimens for rituximab. C-trough as well as AUC have shown non-inferior exposures in the NHL population as well as the CLL population across the established IV dosing regimens and schedules, and across the entire body surface area range.

Pharmacodynamic results extend on these PK results and demonstrate highly consistent and durable depletion of B-cells, as well as repletion kinetics following discontinuation of rituximab during the entire course of treatment with either rituximab IV or subQ. And therefore, the PK and PD of rituximab subQ has been established.

With this, I'll now hand over to Dr. Axel Boehnke who will discuss the clinical efficacy and safety results. Thank you.

Applicant Presentation - Axel Boehnke

DR. BOEHNKE: Thank you, Dr. Morcos.

Good morning, ladies and gentlemen. My name is Axel Boehnke, and I'm the global development team leader for subcutaneous rituximab. To me, the significance of subcutaneous rituximab is twofold. First of all, patients will have to spend less time in the clinics, and therefore they will have more time to go on with their lives.

This is the main reason why there's a strong preference for patients for subcutaneous rituximab, and I'm going to share with you the data in the course of this presentation.

The second significance of subcutaneous rituximab is, because it requires patients to spend less time in the clinics, resources are freed up. And in this context, subcutaneous rituximab will help patients to have timely access to therapy, also at times of existing and worsening IV chair capacity constraints around the world, including the United States.

So let's continue. This is an orientation

of where we are in the presentation. Dr. Morcos has just presented to us how we have established PK non-inferiority of subcutaneous rituximab. And my task is now to share with you how we have established clinical comparability in terms of efficacy and safety, and how we have investigated the satisfaction and preference of the patients for the route of administration. I would like to pick up directly where Dr. Morcos has ended.

After finding and confirming the subcutaneous rituximab doses, achieving PK non-inferiority, we have expanded the clinical development program as shown on the right-hand side of the slide. We have randomized additional patients into the SABRINA study, and we have also initiated two additional studies, the MabEase study and the PrefMab study in order to investigate efficacy, safety, and patient reported outcome. I would like to begin with efficacy, and I'm going to show you the three studies that we have used in order to investigate efficacy.

Before we go into the details of the study,

a brief word on the color coding throughout this presentation. Blue represents subcutaneous rituximab and green indicates intravenous rituximab.

All studies were conducted in standard of care clinical setting in which intravenous rituximab is approved. All studies were conducted in head-to-head comparisons.

On the top of the slide, you see the SABRINA study, which was conducted in first-line follicular lymphoma patients. Patients were randomized to receive either subcutaneous rituximab or intravenous rituximab in combination with standard chemotherapy, which was given for 8 cycles over a duration of 6 months.

The patients that have responded to the combination immunochemotherapy continued monotherapy treatment with single-agent delivery as per the initial randomization for 12 cycles over a course of 2 years.

Below the SABRINA study, you see the MabEase study, which was conducted in first-line diffuse

large B-cell lymphoma patients. Patients were again randomized to receive either subcutaneous rituximab or intravenous rituximab in combination with standard chemotherapy in this based on malignancy. Patients received again 8 cycles of combination immunochemotherapy over a course of 6 months.

At the bottom of the slide, you see the SAWYER study, which was conducted in first-line CLL patients. Also, here patients were randomized to receive either subcutaneous rituximab or intravenous rituximab in combination with the standard of care chemotherapy in this clinical setting. Patients received 6 cycles of treatment over 6 months.

Important to notice, and as mentioned by Dr. de Claro and Dr. Valente, irrespective of the randomization, all patients were treated with intravenous rituximab at the cycle 1. The reason for this is that we wanted to maintain the option of slowing down or stopping the infusion in case of infusion related reactions.

I will go on now to share with you the efficacy results, and I will start with the end-of-induction response rates, which have been the primary endpoints for the SABRINA and for the MabEase study, and the secondary endpoint for the SAWYER study.

Across the treatment arms, we are seeing comparable overall response rates and complete response rates with 95 percent confidence intervals that are narrow and overlapping, indicating that there are no clinically meaningful differences of subcutaneous and intravenous rituximab to induce responses.

We have also investigated time-to-event related endpoints, including progression-free survival and overall survival. In the next consecutive slides, I'm going to share this data with you. I will begin with progression-free survival.

On the top of the slide, you see the progression-free survival for the SABRINA study on the left, with a median follow-up time of

37 months, and for the MabEase study on the right with a median follow-up time of 28 months. The bottom of the slide, you see the progression-free survival Kaplan-Meier curves for the SAWYER study with a median follow-up time of 36 months.

The Kaplan-Meier curves are overlapping. The point estimates for the hazard ratio are between 0.84 for the SABRINA study and 1.23 for the MabEase study. All studies with 95 percent confidence intervals for the hazard ratio include one.

Altogether, this shows that the progression-free survival of subcutaneous and intravenous rituximab are comparable, consistent across three studies. The progression-free survival results are consistent with the overall survival Kaplan-Meier curves, which are displayed in this slide.

So I would like to summarize the efficacy by saying that consistent in three independent studies, we have seen across the treatment arms comparable end-of-induction response rates,

comparable progression-free survival, and comparable overall survival, showing that there are no clinical differences in terms of efficacy of the subcutaneous and the intravenous rituximab in IV-approved indications.

I will now like to continue with the safety results, and again by showing you the study designs of the study contributing to the safety databases.

This is a complex slide, but I'm sure you all remember the study designs from the previous slides that we have shown in this presentation, and I would like to make just three points with this slide.

The first is that all the studies have been head-to-head comparison studies. Studies that were conducted in similar clinical settings were pooled for the safety events, and this means that we have pooled the non-Hodgkin's lymphoma monotherapy safety events from the SparkThera study and from the SABRINA study, as highlighted by the grey box on the top right of the slide.

We have also pooled non-Hodgkin's lymphoma

combination immunochemotherapy safety data from the induction phases of the SABRINA study and of the MabEase study, as you can see in the orange box in the middle of the slide.

The third point I would like to make is that the randomization for the MabEase study was done using a 2 to 1 randomization. This is important to bear in mind when we are in a few moments looking at the safety results. And I'd like you to focus on the percentages rather than the absolute number of patients experiencing result because of the higher number of patients enrolled into the subcutaneous arm.

So let's have a look at the safety results. This table shows you the overall safety results and shows you that safety of subcutaneous rituximab and intravenous rituximab are comparable.

Let's now have a look at where we see numerical differences. There is in the combination immunochemotherapy treatment setting a slightly higher frequency of grade 3 or greater adverse events and serious adverse events. Main drive is

for these numerical differences are neutropenia, and infection. Both are known, common, and manageable side effects in particular during the combination chemotherapy phase.

Differences in these safety events did not translate into any differences of adverse events leading to treatment discontinuation, which is an important point to make for this lifesaving drug.

Important to notice that in the non-Hodgkin's lymphoma monotherapy clinical setting, there are no differences in terms of safety events whatsoever. And furthermore, if we now are looking at the right side of the slide, we can also see that there are no differences in terms of safety event under combination chemotherapy CLL clinical setting.

I would like to now draw your attention to the very bottom of the table where we have displayed the administration-related reactions, which have been investigated as an adverse event of special interest when we are comparing the same molecule given via two different routes of

administration.

Administration reaction have been defined as adverse events occurring within 24 hours and assessed by the investigator to be related to study drug, meaning to either IV rituximab or subcutaneous rituximab.

During the monotherapy NHL clinical setting, we see differences of administration-rated reactions. These differences are driven by mild to moderate, local injection site reactions, and include mild swelling, mild erythema, and mild pain. This is exactly the administration-rated reaction profile that one would expect from drugs given via the subcutaneous route of administration.

These expected differences do not impair or affect the overall benefit-risk profile of subcutaneous rituximab and is not affecting the patient preference, as you will see in a few moments. So in summary, the safety of subcutaneous and intravenous rituximab is comparable.

I would like now to move on to the patient preference, to the PrefMab study. The PrefMab

study is a large study with 743 patients enrolled. As a matter of fact, this is the largest study ever conducted in hematology, focusing on how patients are experiencing their treatment.

The PrefMab study has a unique design with a crossover. This was needed in order to allow patients to make an informed assessment of their preference for the route of administration after experiencing both routes of administration. Patients were randomized to receive either first subcutaneous, and then intravenous rituximab in combination with standard of care chemotherapy, or the other way around.

The primary endpoint of the PrefMab study was assessed using the PPQ, a straightforward [indiscernible] consisting of three questions. First question, do you have a preference for the route of administration? Second, if yes, how strong is your preference? And if you have a preference, third question, what are the two main reasons for your preference?

As a secondary endpoint, we have

investigated the RASQ in order to comprehensively investigate drivers for the satisfaction of the route of administration of rituximab. I'm going to share with you now the results of the primary endpoint.

Eighty percent of the patients have a preference for subcutaneous rituximab over intravenous rituximab, with more than 70 percent of the patients expressing a strong preference. The main reasons for patients preferring subcutaneous is that it requires less time in the clinic. Additional reasons include it's more comfortable during the administration, feels less emotionally distressing, and is associated with a lower level of injection-site pain. All of these reasons are important reasons to patients.

It is important to notice that the overwhelming preference for subcutaneous rituximab was expressed by the patients despite the fact that the study was conducted during the combination immunochemotherapy clinical setting, meaning that all patients had to receive intravenous

chemotherapy in addition to rituximab.

I would like now to share with you the secondary endpoint, the RASQ results. RASQ results are supporting the primary endpoint, as they are showing that patients perceive subcutaneous rituximab to take away less time from their daily routine and being more convenient.

In addition, the three remaining scales, displayed here in the lower part of the slide, shows that the patients are actually equally satisfied with both formulations in terms of administration-related symptoms and efficacy.

This is a very important point for me to make here, because the goal of establishing subcutaneous rituximab is to provide patients with an improved therapeutic option, however, without taking away the option of the patients to receive intravenous rituximab if the patient wishes so.

I would like to now summarize the clinical development program. The clinical development program builds on the extensive experience of over 20 years of research with intravenous rituximab.

The clinical development program is a large program that has enrolled 2,250 patients into 5 clinical trials conducted across the IV-approved B-cell malignancies.

With a large development program, we have demonstrated 4 key results. We have demonstrated non-inferior exposure after subcutaneous rituximab, and we have demonstrated comparable efficacy of subcutaneous and intravenous rituximab consistent across three studies conducted in IV-approved indications. We have demonstrated comparable safety, and we have demonstrated the clear and compelling patient preference for subcutaneous rituximab.

As Dr. Davies has presented, subcutaneous rituximab is approved by health authorities in the European Union since 2014, and hence we have experience of subcutaneous rituximab outside of clinical trials with more than 34,000 patients receiving subcutaneous rituximab in routine clinical practices. The experience with subcutaneous rituximab in routine clinical practice

are consistent with the results of the clinical development program that I have just presented to you.

I would like now to conclude. While reducing the treatment burden for patients, subcutaneous rituximab has a positive benefit-risk profile that is comparable to that of intravenous rituximab. The substantial evidence that you have seen today supports the approval of subcutaneous rituximab as an important improved treatment option for patients for IV-approved B-cell malignancies.

This concludes the sponsor's presentation, and I would like to thank you very much for your attention.

DR. ROTH: Thank you, Dr. Boehnke.

We'll move on now to the FDA presentations and we will start with Dr. Okusanya to discuss clinical pharmacology.

FDA Presentation - Laure Okusanya

DR. OKUSANYA: Good morning. I will be providing the background on the development pathway for rituximab subQ, our perspective on the

comparative exposure-based PK trials, how these trials address questions regarding the selected subcutaneous doses, and if differences in C-trough have an impact on safety.

Rituximab subQ is a co-formulation of two currently approved drugs, rituximab, for which safety and efficacy has been established for the treatment of patients with non-Hodgkin's lymphoma, and chronic lymphocytic leukemia, and hyaluronidase, for which safety and efficacy has been established for use as an adjuvant to increase the dispersion and absorption of subQ injected drugs. As such, in this context, hyaluronidase acts as an adjuvant to facilitate the absorption of rituximab subQ.

The facilitation of the rapid subcutaneous absorption of rituximab by hyaluronidase was evaluated by the applicant in a mini-pig study where, as shown in this figure, we see a threefold increase in the rate of absorption when rituximab was co-administered with hyaluronidase compared to rituximab alone.

In humans, we can also see that it facilitates the subcutaneous absorption of large volumes of fluids. As shown in the left panel, we see the before and after pictures of immunoglobulin G administered subcutaneously without hyaluronidase. We note the large subdermal bump observed with 10 mLs of fluid. However, as shown in the right panel, the co-administration of the same volume with hyaluronidase did not result in a large subdermal bump.

Now, given that rituximab subQ is a different dose, regimen, or dosage form of rituximab, and the safety and efficacy of rituximab administered by the IV route has been established, the applicant proposed a PK bridging strategy for the development of rituximab subQ.

Such development approach is consistent with the FDA's evidence for effectiveness guidance, which indicates that effectiveness may be shown without the use of efficacy trials in certain cases.

This approach of PK bridging has been used

in the development and approval of a number of drugs. For example, the approval of an IV route of administration for asparaginase Erwinia chrysanthemi; the approval of the intravenous formulation of temozolomide based on data from temozolomide tablets; the approval of the extended release carvedilol based on data from carvedilol tablets; and also the approval of nitroglycerin powder based on data from the nitrolingual pump spray. In all these cases, PK was pivotal for approval, and all of these instances are readily translatable to the current application.

Now, for chronically administered drugs, particularly antibodies, trough drug concentrations and/or area under the exposure curve, commonly known as AUC, are commonly correlated with efficacy.

Rituximab concentrations, specifically C-troughs after IV dosing, has been correlated with overall response rate and PFS by certain investigators. Now given that clinical efficacy has already been demonstrated by rituximab

administered intravenously, achieving the same or higher rituximab exposures as the subcutaneous dosing is expected to result in similar efficacy.

In this context, rituximab C-trough after IV dosing can serve as the reference threshold required for efficacy. As such, rituximab subQ C-troughs equal to or greater than that observed after IV dosing is an acceptable endpoint for PK bridging trials.

When assessing the adequacy of the PK data after established efficacy of rituximab subQ, by leveraging data from rituximab IV, we evaluated the following questions.

One, did the proposed dose SubQ doses of 1400 and 1600 milligrams provide adequate exposure relative to the exposures obtained following rituximab IV doses of 375 and 500 milligrams per meter squared?

Two, do the proposed doses of 1400 and 1600 milligrams provide adequate systemic exposures across all body surface sizes for their respective indications?

Three, do differences in C-trough between rituximab subQ and rituximab IV lead to differences in safety?

In order to answer our questions, we evaluated three trials used for the dose selection and dose confirmation. SparkThera was a dose selection and dose confirmation study to determine a rituximab subQ dose that will yield comparable serum C-troughs to the established IV doses in follicular lymphoma maintenance phase.

SABRINA was a dose confirmation study to demonstrate equal or higher rituximab C-troughs after subQ administration compared to IV rituximab in the follicular lymphoma induction phase and also compare the overall response rates between rituximab subQ and rituximab IV at the end of induction.

The SAWYER study was a two-part dose finding and dose confirmation study to determine and confirm a rituximab subQ dose that will yield comparable serum C-troughs to the established rituximab IV dose in patients with CLL.

The dose selection study was conducted in the follicular lymphoma maintenance population. After one cycle of rituximab IV, patients were given a single subcutaneous dose of rituximab subQ at one of three body surface area adjusted doses of 375, 365, and 800 milligrams per meter squared.

The 800 milligrams per meter squared subQ dose showed equal or higher C-troughs compared to the 375 milligrams per meter squared IV dose. And as the applicant has stated, modeling and simulation showed that the 1400-milligram dose is expected to have C-trough values that are equal to or higher than that observed after the 375 milligrams per meter squared IV dose.

This dose was subsequently evaluated by randomizing patients to receive either 1400 milligrams subQ or 375 milligrams per meter squared IV every 2 or 3 months as part of their maintenance therapy. The box plot shows the C-troughs of cycle 2 of the maintenance phase for the 2 and 3 months maintenance regimens.

The C-troughs of the 1400-milligram subQ

dose was equal or higher than that for the 375 milligrams per meter squared IV dose for both dosing regimens. These results of cycle 2 were consistent for the duration of the study.

The effectiveness of the 1400-milligram dose was further confirmed in the SABRINA study. The primary objective was to demonstrate equal or higher rituximab C-troughs after subQ administration compared to IV rituximab in the follicular lymphoma induction setting.

In this study, patients were randomized 1 to 1 to rituximab IV or rituximab subQ. All patients received rituximab IV 375 milligrams per meter squared in cycle 1, followed by IV or subQ doses in the subsequent cycles.

To evaluate the differences of C-trough between the IV and subQ arms, the ratio of the geometric means of the subQ to IV C-troughs before each cycle dose was calculated. As shown in the figure where the X-axis represents the day 1 of each cycle, and Y-axis represents the geometric mean ratio of the subQ to IV C-troughs and the

90 percent confidence interval, the geometric mean ratios was consistently higher than 1 after the initial IV dose in both the induction and maintenance phases.

This supports the applicant's claim that the 1400-milligram subQ achieved equal or higher C-troughs than the 375 milligrams per meter squared IV dose.

The dose selection for patients with CLL was conducted in the part 1 phase of the SAWYER study. In part 1, the dose selection stage, after receiving 5 cycles of rituximab IV, at cycle 6, IV rituximab was replaced by a single subQ dose of rituximab of either 1400, 1600, or 1870 milligrams. Evaluation of the C-trough values after subQ dose, represented on the Y-axis, showed that the C-troughs after subcutaneous doses were equal to or higher than that after the IV dose in the previous cycle.

Part 2 of this study confirmed the selected dose in patients with CLL. The primary objective of this part was to demonstrate equal or higher

rituximab C-troughs after subQ administration compared to IV administration. In this part, patients were randomized 1 to 1 to receive rituximab IV 500 milligrams per meter squared or rituximab subQ 1600 milligrams to compare the rituximab C-troughs after IV and subQ dose.

The ratios of the geometric mean of the subQ to IV C-troughs before each cycle was also calculated to evaluate the differences in C-trough between IV and subQ arms.

As shown in the figure where the X-axis represents the day 1 of each cycle and the Y-axis represents the geometric mean ratio of the subQ to IV, the geometric mean ratios were consistently greater than 1 after the initial IV dose as well.

This supports the applicant's claim that the 1600 milligrams subQ achieved equal or higher C-troughs than the 500 milligrams per meter squared IV dose in patients with CLL.

The transition from a body surface area based dosing regimen to a fixed dosing regimen may result in the under dosing of patients with large

body surface areas. As such, a comparison of the C-trough values after subQ and IV doses were evaluated across body surface areas. As shown in the figure, for the 1400 mg subQ dose compared to the 375 milligrams per meter squared IV dose in the SABRINA trial, the C-trough values after IV dose was relatively flat.

The horizontal line represents the median C-trough concentration after the IV dose. We note that the trough values after the subQ dose were typically higher than the median trough values after the IV dose across a range of body surface areas, and the C-troughs after subQ dosing provided reasonably consistent exposures across all body surface area sizes relative to the IV dose.

A similar result was observed with the 1600-milligram subQ dose when compared to the 500 milligrams per meter squared IV dose. This supports the applicant's claim of the adequacy of the fixed dose across body surface areas.

Given that the subQ doses resulted in equal or higher C-trough concentrations compared to the

IV dose, the impact of exposure on safety was evaluated. The relationship between exposure and neutropenia, adverse events, serious adverse events, and grade 3 plus adverse events were explored.

No significant relationships between exposures and these evaluated safety endpoints were observed. However, small numerical differences in safety events were observed between the IV and subQ regimens. More details on these differences will be addressed by Dr. Schwarsin.

In summary, fixed 1400- and 1600-milligram subQ doses of rituximab lead to equal or higher rituximab C-troughs than rituximab IV. Fixed subQ doses provide consistent exposures relative to the body surface area based IV doses across the wide range of body surface area, and no significant relationships between exposure and safety events were observed.

FDA Presentation - Jingjing Ye

DR. YE: Good morning. My name is Jingjing Ye. I'm a statistical reviewer in FDA. I

will present FDA efficacy evaluation of rituximab subcutaneous injection.

Here is an overview of the study submitted for evaluation. Clinical efficacy was evaluated in four randomized clinical trials, however, there were no prespecified hypotheses to test for efficacy in any of the studies. Therefore, the objective here is to describe the observed data and not to make inferential statements.

In the two main clinical studies, SABRINA and MabEase, the primary endpoint is response rate. There are also multiple secondary endpoints proposed in each of the clinical studies and there are no adjustments for multiplicity.

Here are the summaries of the four clinical studies listing the patient population, randomization ratio, number of subjects per treatment arms, primary endpoint and secondary endpoints in the studies.

The two highlighted studies are the two main clinical studies. SABRINA in patients with follicular lymphoma and MabEase in patients with

diffuse large B-cell lymphoma. Both of the studies have primary endpoints of investigator-assessed response rate at the end of induction therapy. The secondary endpoints are shown in the table.

The third study, PrefMab, is the patient preference study in patients with follicular and diffuse large B-cell lymphoma. This study will be presented by patient reported outcome reviewer, Dr. Vishal Bhatnagar. In this presentation, I will focus on time-to-event endpoints of PFS, progression-free survival, and OS, overall survival results.

The last study, SAWYER, is in patients with chronic lymphocytic leukemia, CLL. The primary objective of this study was to establish non-inferiority based on the primary PK endpoint C-trough between subcutaneous injection and IV. This was already presented by clinical pharmacology reviewer, Dr. Lanre Okusanya, earlier. We will present the results of secondary endpoints, response rate including CR, CRi, and PR.

The objective of FDA's evaluation of

efficacy is to ensure the efficacy is not compromised by using subcutaneous injection instead of IV.

The primary endpoints of investigator-assessed response rate for the two main clinical studies are summarized in this table. The response rate for the subQ and IV arms are listed in the third and fourth column of the table. The difference between the response rate was the corresponding 95 percent confidence interval is listed in the fifth column of the table.

The response rate ratio between subQ and IV and the corresponding 95 percent confidence interval is listed at the last column in the table. Please note, a response rate ratio greater than 1 favors the subQ arm.

For the SABRINA study, the difference between subQ and IV response rate is negative 0.5 percent with a lower 95 confidence interval at negative 7.7 percent. The response ratio is 0.99 indicating that the estimated probability of patients achieving ORR in patients who received

rituximab subQ is 99 percent of the estimated probability in those who received rituximab IV.

For MabEase study, the difference between subQ and IV response rate is 4.9 percent with lower 95 percent confidence interval at negative 3.6 percent. The response rate ratio is 1.12 favoring the subQ arm and 95 percent confidence interval covering 1. Overall, the response rates are comparable between the subQ and IV arms.

This slide shows the results of secondary endpoints for SABRINA study, which include the complete response rate at end of induction, objective response rate at end of maintenance, and complete response rate at end of maintenance. The number of subjects achieving the response and the total number of patients in the respective evaluation are given in the parentheses.

The complete response rate at the end of induction is the same between subQ and IV arm, therefore, the difference is zero. The difference between subQ and IV arm is negative 0.2 percent for response rate at the end of maintenance. The

difference between subQ and IV arm is negative 5.6 percent for complete response rate at the end of maintenance.

All 95 percent confidence intervals of the response rate are covering zero. The response rate ratio is 1 for the first two results, and 0.9 for the complete response rate at the end of maintenance, indicating slightly decreasing in response rate in subQ arm. All confidence intervals covering 1. Overall, the response rates are comparable between subQ and IV arms.

For SABRINA study, this slide shows a Kaplan-Meier plot of overall survival. The red line is subQ arm and blue line is the IV treatment arm. The number of subjects at risk are given at the bottom of the plot. As can be seen from the plot, the two survival curves stay close to each other and cross at several time points.

The table superimposed in the plot lists the number of events in the subQ and IV arms in the second and third column. The percentage of patients with events are in the parentheses. The

stratified hazard ratio estimated using Cox proportional hazard model are in the fourth column, and the survival rates are 2 years using Kaplan-Meier survival estimates are listed in the last two columns.

PFS results are included in the table for completeness, and while the PFS curves are not presented here, similar pattern as the OS curve were observed.

As can be seen from the results, the number of events and survival rates at two year are similar between the subQ and IV arms. Overall, the results are comparable between the subQ and IV arms.

For the MabEase study, similar as previous slide, the Kaplan-Meier plot of the overall survival are displayed along with the table reporting results of secondary endpoints, PFS, and OS. The table is structured the same as in previous slides of SABRINA study. Again, from the plot, the curves stay close together and cross at several time points.

As a reminder, for the diffuse large B-cell population, the trial was randomized 2 to 1. As seen from the table, the number of events is higher in the subQ arm than the IV arm. The progression-free survival rates at 2 years are about 7 to 8 percent lower in subQ arm compared to IV arm, however, for OS, the survival rates at 2 years are similar.

The hazard ratios are stratified by stratification factor in the trial, and the point estimates are all above 1 in this population, flipped from the previous SABRINA study in follicular lymphoma where hazard ratios are less than 1. However, all the confidence intervals include 1. Overall, the results are comparable between the subQ and IV arms.

The response rate in the SAWYER study is in patients with CLL are presented in the top table in this slide. The response rate in the IV and subQ arm was 95 percent confidence interval are given in the second and third column. The difference of response rate between the subQ and IV arm is given

in the fourth column. The response rate ratio is given in the last column.

As shown in the table, in this study the response rate was higher for patients receiving subQ by 4.6 percent compared to patients receiving IV. The 95 percent lower confidence interval is negative 7.2 percent for the difference in response rate. The response rate ratio is 1.06 favoring subQ arms, and the 95 percent confidence interval includes 1.

The table below shows the results of time-to-event endpoints of PFS and OS. These results were reported by the applicant, using time-to-event data that are now mature. Because FDA does not have patient level data, these results have not been confirmed. Overall, efficacy results are comparable between subQ and IV arm given the assumption that the time-to-event results can be confirmed.

Summarizing the four studies, all efficacy results are descriptive. The data tend to show that subQ and IV arms are comparable, and efficacy

results are similar across studies.

FDA Presentation – Alexandria Schwarsin

DR. SCHWARSIN: Hello. My name is Alexandria Schwarsin, and I will present the agency's safety findings. The discussion of safety is descriptive and will focus on the two phase 3 trials conducted with the 1400-milligram dose, SABRINA in follicular lymphoma, and MabEase in diffuse large B-cell lymphoma, and the SAWYER trial done in patients with chronic lymphocytic leukemia using the 1600-milligram dose. Of note, these three trials were done in the first-line setting.

Common treatment emergent adverse events on the rituximab subQ arm, defined as occurring in greater than 25 percent, were neutropenia and nausea in follicular lymphoma; neutropenia in diffuse large B-cell lymphoma; and neutropenia, nausea, pyrexia, and injection site erythema in CLL. In evaluating treatment-emergent adverse events at the preferred term level, there were no major differences.

In the table, listed are the three trials

and below are the adverse events in greater than 10 percent of patients that are increased over 5 percent for all grades on the rituximab subQ arm.

The largest trial in the middle column, MabEase, in patients with diffuse large B-cell lymphoma, did not demonstrate any adverse events with a difference greater than 5 percent for all grades. However, neutropenia, grades 3 and 4 only, was increased 6 percent.

For the other two trials, given the different administration routes, an increase in the adverse events of injection site erythema and injection site pain is not unexpected. If you remove these, nausea and cough were increased approximately 9 percent on the rituximab subQ arm in SABRINA, and pneumonia was increased 6 percent.

For CLL, the SAWYER trial, neutropenia was increased 6.3 percent, erythema 8.6 percent, and pyrexia 7.1 percent. In conclusion, at the preferred term level for the three trials, we are not seeing major differences in overall adverse events except for injection site reactions.

An adverse event or suspected adverse reaction is considered serious if it results in death, is life-threatening, results in hospitalization, or prolongation of existing hospitalization, among other criteria.

In looking at serious adverse events across the three trials, the only non-fatal serious adverse event increased over 2 percent on any of the three trials on the rituximab subQ arm was febrile neutropenia and pyrexia. Febrile neutropenia was increased 0.3 percent on the follicular lymphoma trial, 2.2 percent on the diffuse large B-cell trial, and 6.1 percent on the CLL trial. Pyrexia was increased 2.4 percent in CLL.

While the numbers are relatively low, it should be kept in mind that this increase is associated with hospitalization. Thus, there may be a potential for an increased risk of hospitalization associated with febrile neutropenia with rituximab subQ.

An important question given the higher drug

concentrations associated with rituximab subQ is, is the risk of a non-fatal serious adverse event increased given the higher drug concentrations associated with rituximab subsequent? In evaluating patients with at least 1 non-fatal serious adverse event, there was not a consistent across the three trials.

In looking at the three trials on the table, below are the percent of patients with at least 1 non-fatal serious adverse event on the rituximab IV arm, followed by the rituximab subQ arm with the third column under each trial being the difference between the two arms.

For the 1400-milligram dose used in the follicular lymphoma trial and the diffuse large B-cell trial, there is a 3.6 percent increase and a 5.6 percent increase for these two trials, respectively. For the 1600-milligram dose in chronic lymphocytic leukemia on the SAWYER trial, the rate of patients having at least one serious adverse event was lower in the rituximab subQ arm. Thus, a consistent increase across the three trials

is not seen, but a slight increase is seen in follicular lymphoma and diffuse large B-cell lymphoma.

In reviewing the laboratory data, there is an increase in neutropenia across the trials. Neutropenia as a laboratory value was increased 3.1 percent in follicular lymphoma, 5.1 percent in diffuse large B-cell lymphoma, and 9.4 percent in chronic lymphocytic leukemia.

The increase across the trials is also seen when looking at grades 3 and 4 neutropenia only. Grade 3 and 4 neutropenia was increased 7.6 percent in follicular lymphoma, 2.1 percent in diffuse large B-cell lymphoma, and 5.3 percent in chronic lymphocytic leukemia. While this alone is not clinically significant, a natural question following this is, is there an increased risk of infection?

As shown in the previous slide, there's not a major increase when looking at specific infections at the preferred term level. When looking at non-fatal infections overall at the

system organ class level, there is 4.1 percent increase in follicular lymphoma, a 6.7 percent increase in diffuse large B-cell lymphoma, and a 7.0 percent increase in chronic lymphocytic leukemia.

When looking at non-fatal infections that were classified as serious adverse events, a consistent increase is seen across the three trials: 5.2 percent in follicular lymphoma, 6.1 percent increase in diffuse large B-cell lymphoma, and a 1.7 percent increase in chronic lymphocytic leukemia.

Administration site reactions were defined in the trials as occurring within 24 hours of administration of the drug and attributed to the drug by the investigator. In looking at these, the majority of these reactions overall for rituximab subQ were injection site erythema and injection site pain.

In looking at these two reactions reported as adverse events, the rates across the trials are displayed. The lowest in the 2 to 3 percent range

was in diffuse large B-cell lymphoma, with the higher end of the range across the trials at 25.9 percent and 16.5 percent in chronic lymphocytic leukemia for injection site erythema and injection site pain.

With the different routes of administration, these reactions were not reported in the rituximab IV arm. The reason for the variation among the three trials is unclear.

In conclusion, there were no major differences between the two arms in the three trials, aside from administration site reactions, an increased risk of neutropenia associated with a possible increased risk of infection.

Rituximab IV is frequently used in first and later lines of therapy. The trials discussed in the safety evaluation studied the use of rituximab subQ in the first-line setting. Rituximab subQ is associated with higher drug concentrations, which may be more of an issue with repeated use. The effect of this in subsequent lines of therapy is unknown. Thank you.

FDA Presentation - Vishal Bhatnagar

DR. BHATNAGAR: Good morning. I will briefly discuss the results of the PrefMab trial, which the applicant is using to base patient preference and patient-reported outcomes.

The PrefMab trial was an open-label, multicenter trial designed to evaluate patient preference between subcutaneous and intravenous administration of rituximab. Subjects had diffuse large B-cell lymphoma or follicular lymphoma, and were previously untreated. Subjects were to receive R-CHOP, R-CVP, or R-bendamustine per the standard of care for their disease in order to enroll on the trial; 201 sites enrolled subjects in 32 countries.

The primary objective of the trial was to evaluate the proportion of patients indicating an overall preference using the patient preference questionnaire for either the subcutaneous or the intravenous route of rituximab administration.

Three instruments were administered in the trial. The PPQ was the Patient Preference

Questionnaire. The two satisfaction questionnaires were the Cancer Therapy Satisfaction Questionnaire, or CTSQ, and the Rituximab Administration Satisfaction Questionnaire known as RASQ. Note all instruments, including the PPQ, were administered to subjects in written form and without assistance from healthcare providers.

The Patient Preference Questionnaire was a series of three questions and was administered at the end of cycle 6 and 8 of the chemotherapy regimen.

The PPQ is shown here. The questions were, 1, which method administration did you prefer; 2, how strong was the preference; and 3, what the two main reasons were. Subjects could choose from prespecified responses, but there was a section for subjects to provide a write-in response if needed.

The Cancer Therapy Satisfaction Questionnaire was developed from interviews with patients with solid tumors and has been previously used across multiple tumor types. It measures patient satisfaction across three domains:

expectations of therapy, feelings about side effects, and satisfaction with therapy.

A sample question is, in general, in the last four weeks, how often did you feel that cancer therapy was worth taking even with the side effects? And the responses were always, most of the time, sometimes, rarely, or never.

The RASQ is a 20-item questionnaire measuring the impact of the mode of the treatment administration on five domains: physical impact, psychological impact, impact on activities of daily living, convenience, and satisfaction. A sample question includes, how do you feel about the amount of time the treatment takes? Too short, just right, or too long.

This is the design of the trial. Subjects were randomized to either arm A or B. In the first cycle of both arm A and B, rituximab was administered intravenously. The green boxes are cycles in which subjects were administered rituximab intravenously, and the blue boxes were cycles in which subjects were administered

rituximab subcutaneously.

The satisfaction questionnaires were administered during cycles 4 and 8. The patient preference questionnaire was administered at the completion of cycles 6 and 8.

In terms of results, following cycle 6 and 8, approximately 80 percent of subjects preferred the subcutaneous injection, regardless of the order of rituximab administration. The majority of subjects who had a preference at cycle 6 retained their preference at the end of cycle 8.

In terms of reasons for their preference, subjects most frequently chose requires less time and feels more comfortable. Note that the percentage totals add up to greater than 100, as subjects were allowed to pick two reasons.

The CTSQ results were similar and comparable in all three domains between IV and subQ. Although the RASQ was similar in content, subQ was favored in 4 out of 5 domains. Although the content and timing of the satisfaction tools were similar, the

results were disparate between the two satisfaction questionnaires. A possible reason for the difference between satisfaction questionnaire results is timing of the assessments, as the CTSQ was administered just prior to cycle 4 and 8, while the RASQ was administered immediately after cycle 4 and 8.

The CTSQ and RASQ, which were designed to gauge patient satisfaction with their chemotherapy, had disparate results despite similar content in timing. Another possible explanation for disparate results is that the RASQ and CTSQ may not have been appropriate to gauge satisfaction in this context, as subjects were receiving multiagent chemotherapy.

These instruments were not designed to isolate the effect of rituximab administration, IV versus subQ, in this treatment setting.

Recall period is defined as the period of time patients are asked to consider in responding to a PRO item or question. In PrefMab, subjects were asked to compare the modes of rituximab administration at the end of cycle 6 and 8. After

cycle 8, subjects would be asked to compare their current method of rituximab administration to the mode of administration last received over 3 months prior. Although the recall period between cycle 4 and 8 is long, similar results at cycle 6 and strong retention of preference between cycle 6 and 8 mitigate concerns with the length of the recall period.

In conclusion, the development and administration of the Patient Preference Questionnaire was reasonable in the PrefMab trial. The brevity and clarity of the questions in the PPQ, large sample size, magnitude of effect, and consistency of findings at more than one time point, are strengths of the preference results.

Both the RASQ and CTSQ had limitations and had disparate results despite content overlap in timing. Satisfaction is difficult to assess with multiagent chemotherapy, due to numerous confounders. Therefore, the results of the satisfaction instruments may be unreliable.

To summarize the FDA presentation as a

whole, rituximab subQ achieved equal or higher C-trough relative to rituximab IV. A fixed dosing strategy led to consistent C-trough across all BSA sizes relative to the BSA-based dosing regimen of rituximab IV. Efficacy results were comparable between IV and subQ arms in all clinical trials.

There were no major differences in safety findings between rituximab subQ and rituximab IV. The PrefMab trial was adequate to determine preference for rituximab subQ.

Clarifying Questions to the Presenters

DR. ROTH: Thank you very much.

We're going to move on to clarifying questions to presenters, so when you do ask a question, please state your name first to make it a little bit easier for the poor transcribers of this session. And then if you can identify a particular presenter to direct your question at, then please do so.

If you'd raise your hands, Lauren will write down your name and try to take the questions in order. Maybe if I could take the prerogative here

and start off.

For the sponsor, I'm not quite sure who'd be the appropriate person, maybe Dr. Boehnke since this has to do with toxicity, but I wonder if we could dwell a little bit more, because it was in the presentation, about the low BSA patient.

Number one, I'm not quite sure what low BSA is. I know that's not need, but if you could define that a little bit better. And two, as it refers to frequency of SAEs, is there a threshold BSA level below which we should be seeing, possibly in the label, that may be flat dosing is not a good idea?

DR. VALENTE: So I'll start with the definition of BSA. We divided BSA into three groups based on the patients that were enrolled in the trial. We divided those into tertiles based on the BSA like that.

Overall, as you saw in Dr. Boehnke's presentation, the safety is comparable between the IV and subQ. We did see differences as described by us and the FDA for neutropenic fever and

infections. And these are well-known by physicians who treat patients with lymphoma and CLL, and their successful management is demonstrated by the fact that we didn't have a difference in AEs leading to discontinuations or AEs leading to death.

For your question relating to the smaller BSA patients, I'm going to ask our safety expert, Dr. Ellie Guardino, to provide additional information.

DR. GUARDINO: Hello. I am Dr. Ellie Guardino. I'm a medical oncologist. I'm also the head of safety science oncology at Genentech.

So the safety profile across BSA subgroups, I think this question can be addressed in a number of ways. But where we saw differences was primarily in the chemotherapy combination, and the trends that we see are consistent with what you heard from Dr. Boehnke for the overall safety profile.

The AEs were consistent, and they're known AEs for Rituxan. I think you heard also from Dr. Schwarsin, details on that. And I agree with

the presentation that was given by the FDA. The trends that we see for the lower BSA are the same as we saw for the overall safety population.

Rituxan IV has got a wide therapeutic range. We have a great deal of safety that's known for IV Rituxan. This is an identical drug that's being used in a different route of administration. The wide therapeutic range for IV Rituxan has shown safety across a number of a wide therapeutic or a wide dosing so that safety has been established with the identical therapy.

Additionally, when you look at the monotherapy and the maintenance phase, there's no difference, so we didn't see this increase in -- slide up -- adverse events by subgroup.

There were no differences that were seen for deaths or discontinuation by BSA, and that's shown here. This was described by Dr. Valente that we're looking at the 33 percent in each group for low, medium, and high.

So overall, we've shown comparable safety for the overall patient population. Additionally,

you heard from the PK analysis. And when we look at the exposure-response by safety, we see no correlation between any of our safety events that were looked at, not just the SAE in grade 3 or higher, but actually neutropenia and other safety endpoints, there was no correlation with BSA, with our body surface area or exposure.

Additionally, multivariate analysis that was done in the clinical trials did not differentiate the route of administration with the SAEs and grade 3 or higher adverse events.

So in totality, I feel confident that we have a comparable safety profile and hope that addresses your question. Thank you.

DR. ROTH: Okay. Thank you.

Dr. Harralson?

DR. HARRALSON: I'm looking at the FDA slide 18 for Dr. Okusanya, and the term they use is "consistent exposure." And as I look at that, it looks highly variable, and it's consistent in the sense that it's above a predetermined level, but it's highly variable. And if you look right around

the 1.5 BSA area and look up, it's 10 times higher.

I also obviously see that in the SABRINA data on the sponsor's slide 33. The lower end of body surface areas have really highly variable serum concentrations for the given dose.

I guess I wouldn't argue that it's not enough, but I wonder if that's really consistent. And given that you have a patient that you may give the IV administration to, that you accurately estimate body surface area and then make that adjustment, I'm just wondering why wouldn't you do that with the subQ injection if you are simply injecting a certain volume.

So I know that's a wide-ranging question, but by consistent, do you simply mean it's above a certain baseline?

DR. VALENTE: So we very carefully consider the change to fixed dose, because we wanted to decrease the treatment burden, as we've stated, but we also wanted to ensure that patients had an adequate dose across all BSA ranges. That's what you see here in this slide. So that consistency

that we're showing is across -- if you consider the median and the confidence intervals and compare that to the IV exposure.

I think part of your question was also, why didn't we just use a BSA adjusted dose? That's been done for rituximab IV. That was historically done at the time rituximab was developed. All cancer therapies were given by a body surface area or weight-adjusted dosing because that was the first antibody. But newer antibodies are now being given, but with fixed dosing, including the new checkpoint inhibitors, Perjeta for breast cancer, other B-cell directed therapies like Gazyva, as well for lymphoma in CLL all fixed dosing.

DR. ROTH: Dr. Karara?

DR. KARARA: My question to the sponsor relates to the C-trough values that were obtained in CLL patients in stage 1 of the dose finding part of the SAWYER study. This is the part where they decided on the 1600-milligram dose, reference to table 7 of the FDA briefing book on page 23.

My question relates to that cohort of the

1600 milligrams and the variability associated with the geometric mean values being in the order of about 100 percent. I understand obviously there was a small cohort, only 17 patients, but my question, was there any particular patient characteristics that may have contributed to that variability? For example, did these patients exhibit a larger tumor load than other patients in that group?

DR. VALENTE: I'm going to ask Dr. Morcos, our pharmacologist, to further elaborate on that.

DR. MORCOS: Peter Morcos, clinical pharmacologist. So what's important to recall is that in stage 1 of both SparkThera and SAWYER, patients were receiving previous cycles of IV treatment and then a switch for one cycle of subcutaneous. So there's some underlying variability associated with prior cycles, residual concentrations.

This is why in the sponsor's presentation a modeling simulation approach was used to both understand the PK, as well as used to determine the

fixed dose that would be appropriate based on this.

In terms of the variability in rituximab PK, we've conducted population PK analyses to identify sources of variability and quantify them. Results from those analyses indicate that the main source of variability comes with BSA, as one would expect. However, in the extreme BSA patients, those are only modestly different actually than the mean BSA in the population.

An additional source of variability is baseline tumor size, as you would expect with a monoclonal body that targets, for example, a tumor. So are those are the two main sources of variability.

DR. KARARA: At this stage, these samples were taken at cycle 6, I believe. What would be the level of involvement of target-mediated drug disposition at this stage? Is there any involvement at this stage, or most of the CD20 cells would be wiped out at that point?

DR. VALENTE: I'm going to ask Dr. Morcos to answer your question.

DR. MORCOS: Peter Morcos, clinical pharmacologist. So by cycle 6 in the CLL population, based on our population PK analyses, suggest that the time vary in clearances associated with the tumor or the target should be negligible by that time. So the majority of the clearance at that point is just the linear catabolism of monoclonal antibodies.

DR. ROTH: Did that answer your question?

(Dr. Karara nods in affirmative.)

DR. ROTH: Okay. Dr. Burstein?

DR. BURSTEIN: Two real-world questions for the sponsor. The first is that the trials all had a first dose, IV dosing of rituximab, presumably to make sure you didn't have an allergic reaction or you got some dose. It's easy to imagine that might be omitted in ordinary practice. People are sort of not aware of that subtlety.

Are there are data or reason to think that going directly to a subcutaneous product without that one time IV dose would in any way affect outcome, toxicity, anything like that?

DR. VALENTE: We didn't study the first dose as subcutaneous. As you stated, we left it as IV because of the infusion reactions and wanting to be able to adjust the dose or delay or stop it if needed. And we've taken precautions in the development of this product to minimize the risk of the dose being delivered erroneously, and we've done that with packaging, distinct packaging for the outside package and the vials as well. I can show that if you would like.

In our postmarketing experience, as we've mentioned, we've treated over 34,000 patients. There have been a few patients who did receive the subcutaneous product IV for their first infusion, and we haven't seen any safety issues from that administration. So we haven't studied it, but we've seen a few cases when that has occurred.

DR. ROTH: If I could just piggyback on Dr. Burstein's comments. So you treat a patient, IV first dose, and they have an infusion reaction, should I have any pause before giving the next dose subQ?

DR. VALENTE: All of our studies allowed patients with any type of infusion reaction, for the first infusion, to go on to the subcutaneous dosing. So no, I wouldn't have any concern.

DR. ROTH: Okay. Thank you.

DR. BURSTEIN: In follow-up, you both alluded to the postmarketing experience. I gather the product is approved in Europe, Australia, UK, perhaps elsewhere.

Is there something else to be learned about administration of the drug from that experience, which is more than 10 times the number of patients treated on these trials in terms of real-world challenges with administration, or a successful installation of the subcutaneous product, or anything else that you've encountered in your postmarketing data that would bear on reliable use of the product in the commercial market?

DR. VALENTE: I'm going to ask Dr. Davies, who's actually administered the product, and it's available in the United Kingdom, for his thoughts there.

DR. DAVIES: Andrew Davies, medical oncologist from Southhampton in the UK. I think this is a really important question about real-world experience. I've delivered several thousand doses now of subcutaneous rituximab.

I think with our modern prescribing systems, the safe delivery of the first intravenous dose is absolutely deliverable. So you can set up appropriately so you always give your first dose intravenously.

We've learned a lot through education of the teams about delivery of the injection, because you can imagine for nursing staff, presentation of an 11.6 mL injection, first off, is something of a challenge before they've done it.

Actually, through education programs, we have made the nursing staff very comfortable with it, just as comfortable as delivering it with people who are abdominally well-covered, as thin people as well. And I have known of no patient who wished to switch back from the subcutaneous formulation, having had exposure to it.

DR. ROTH: Thank you. Dr. Uldrick?

DR. ULDRICK: Thanks. One of the things in evaluating the safety, it would be helpful to better understand the neutropenia findings. And I was wondering if you have more data on the association with the concentration of rituximab and in the estimates of whether or not some of this neutropenia was previously described late-onset neutropenia that's been seen with rituximab?

My specific question is, is there an association between the C-trough and grade 3/4 neutropenia, and do you have a point estimate of late-onset neutropenia?

DR. VALENTE: I'm going to ask Dr. Morcos to answer that question.

DR. MORCOS: Peter Morcos, clinical pharmacologist. So we've investigated the relationship between rituximab exposure in various events, including neutropenia. If I can pull up PK007 please and exposure safety from SABRINA? Slide 4, please?

So this is the investigation of the

relationship between rituximab exposure and neutropenia for the subQ and IV arms. These are, again, distribution figures, which illustrate the distribution of exposure for patients reporting various grades of neutropenia.

As illustrated on the slide, for both the IV and subQ arm, there's no correlation between the relationships of distributions of exposure and the outcomes of neutropenia events across the various grades. Hope that helps. Thank you.

DR. ROTH: Dr. Waldman?

DR. WALDMAN: Yes, thanks. I want to come back or continue on the theme of safety. I'm trying to connect dots that are not obviously connecting, and that I hear are not connected, but these things are not making sense, to me at least.

The concern is will a skinny patient who's receiving combination therapy with a fixed dose of the formulation, are they at greater risk of experiencing greater than grade 3 or serious AEs? That's the question.

It seems to me that skinny patients

have -- generally, patients with fixed doses are getting higher exposures by C-trough and AUCs, at least from the data that we have. That's a good thing for therapy. It may not be the perfect thing for SAEs.

It seems that there's a relationship between BSA and C-trough. From the agency's data, it seems that there is a relationship between C-trough and greater than grade 3 or serious AEs. You have a plot in the data that shows a relationship.

So if you string those things together, you have to ask the question, thin people with low BSAs receiving fixed doses that are getting combination chemotherapy, are they at greater risk for experiencing grade 3 or greater or serious SAEs? That's the question.

I know it's a lot of points on a page that I'm stringing together, but it's a safety question.

DR. VALENTE: I understand your question, and we have very carefully evaluated that question that you just linked together, that I'm not sure I can repeat.

DR. BURSTEIN: That's okay.

(Laughter.)

DR. VALENTE: I'm going to ask Dr. Morcos again -- we have graphs -- to look at exposure and higher grade AEs.

DR. MORCOS: Peter Morcos, clinical pharmacologist. If we can just pull up the core deck slide on the exposure safety analysis please?

We have investigated, carefully and exhaustively, whether there are relationships between rituximab exposure and safety events in consideration of any exposure differences that may arise between the fixed doses.

What's important to note firstly is, based on the analyses we've done in our population PK analysis, while body surface area is a covariate in the model, the actual Pop PK analysis indicates that in patients with extreme body sizes -- so 2.5 percent of the population in the study, or the 97.5 percent of the population in the study -- the variation in the exposure is about 30 percent of that of the mean exposure in -- of the mean BSA in

those studies.

So the variation with the very large and very small is actually not dramatically large. But nonetheless, we have tried to extensively investigate whether or not there's a relationship between rituximab exposure and safety events.

What I've presented in my slide here is the distribution of exposures following rituximab subQ for various grades of safety events. And as I've tried to illustrate during the presentation, as you can see, the distribution overall across the two populations in NHL in SABRINA and CLL in SAWYER, there's no apparent correlation between patients who did not report a grade 3 or greater safety event in the first column versus those who did.

On this specific consideration of exposure relationship to safety event, there did not seem to be any clear or identified trend to support that.

DR. BURSTEIN: Can I follow-up?

DR. ROTH: Go ahead.

DR. BURSTEIN: So for the SABRINA study, does that break out combination therapy? Does that

include all-comers, combination and mono? Does that include everybody, combination and mono?

DR. MORCOS: Yes.

DR. BURSTEIN: Do you have the data broken out just in combination therapy, because those are the folks that I'm worried about.

DR. MORCOS: So we have the data broken out for induction and for maintenance, so presumably induction means combination, if I understand the clinical [indiscernible] correctly.

If we can just pull up in the exposure safety backup folder, PK007, exposure safety SABRINA, if we just move forward a few slides in that backup folder, I'll tell you when to stop.

This is the SABRINA trial. This is now broken up by grade 3 and greater AEs for induction and maintenance treatment separately. So on the left side is subcutaneous; on the right side is IV. And again, these are distribution figures illustrating patients who reported or did not report grades of safety events with rituximab exposures.

Again, as you can see here, the distribution of exposures for patients who did not report a safety event, however an induction or maintenance for either subQ or IV, did not illustrate any correlation with safety outcomes.

So again, as part of this comprehensive investigation of exposure safety, we did not identify relationships between exposure and safety events for grade 3 and greater AEs, for SAEs, for neutropenia, and for serious infections as part of our investigations. Thank you.

DR. ROTH: We have a number of additional clarifying questions. Why don't we take a 15-minute break and come back, and then finish those before moving on. So let's reconvene at 10:30.

(Whereupon, at 10:14 a.m., a recess was taken.)

DR. ROTH: Let's go ahead and start back up. We have a handful of additional clarifying questions, and we'll start with Dr. Morrow. P.K.?

DR. MORROW: Thank you. Just piggybacking

on Dr. Burstein's questions and the recent questions about safety. We need to ask, based upon your 34,000 patients treated in a real-world setting, whether -- I assume there's no new safety signal, but also if there were any particular patient characteristics, including BSA, that led to any changes in safety findings.

Second question, really quickly, is related to safety, you note the event rates for safety findings in your booklet. Were there any statistically significant differences between the subQ and IV arms?

DR. VALENTE: We do have the 34,000 patient experiences postmarketing. And the data that's collected there is postmarketing surveillance, and we're really dependent on the physician who fills out the form. Overall, we haven't seen any difference in that data and what we've seen in our clinical development program in regards to safety. So we've seen no new safety signals. We haven't looked at specific characteristics from the postmarketing data as filled out on those forms and

safety, but overall, we haven't seen anything new.

I forgot if there was a second question?

DR. MORROW: Just related to whether there was any statistically significant differences in the safety between the two arms within the clinical trials.

DR. VALENTE: Yes. In the postmarketing surveillance -- you're talking about the postmarketing surveillance of the 34,000 patients --

DR. MORROW: In the trials.

DR. VALENTE: Oh, in the trials. You've seen the overall -- Dr. Boehnke showed you the overall safety as part of our presentation, and there wasn't any major differences between the two treatment arms. We pooled the data by combination chemotherapy, so the inductions, the maintenance part for the monotherapy in CLL and across those overall, very similar.

There were some numerical differences that he described, and those adverse events are familiar to the treating physician, the doctors who take

care of lymphoma patients, and it didn't result in any increased adverse events leading to discontinuations or deaths.

Did I answer your question?

DR. PAZDUR: Can I just jump in there? There was no really prespecified hypothesis testing to assign a p-value to, so you really can't talk about statistical significance of these trials.

DR. VALENTE: Thank you.

DR. ROTH: Dr. Klepin?

DR. KLEPIN: Yes, thanks. Heidi Klepin. I'd like to raise another real-world issue with respect to extrapolation of the data from the trials presented to older patients and specifically patients in the 80 and above age group. It's notable in I think the MabEase trial, which was diffuse large B-cell lymphoma, that there was an eligibility cutoff of 80 years, so anybody above 80 wouldn't have been eligible or on that trial.

In the SAWYER trial, it looked like to oldest aged participant was around 76. Of course, we see a lot of patients in clinic that are in the

80 plus range who are treated now with rituximab and would be potentially eligible for this type of therapy, if this moved forward.

So I'm curious, number one, if there was a scientific rationale for limitation on the eligibility in the MabEase trial? And if so, what that was and the implications of that?

Then number two, do you have any signals or data from the real-world experience with respect to safety, particularly thinking about the numerical signal of neutropenia and infection, which for the oldest patients, you could worry would result in more serious complications.

So is there any data that we could hear about in that regard?

DR. VALENTE: So we do have patients -- you pointed out the age, the upper limit of the age range for two of the studies, but in SABRINA we did treat patients up to 86 years of age, and we haven't seen any differences in their outcomes.

I'll ask Dr. Guardino to further comment on the safety data there, and I think it'd be nice if

we also, after that, had Dr. Davies to share this experience with elderly patients in his clinic as well.

DR. GUARDINO: Dr. Ellie Guardino, safety science oncology. So just to comment on the postmarketing data, we do have actually over 35,000 patients that are treated in the postmarketing setting at this point, and we have not had any safety signals, any new findings. The only difference that we really see is in the local cutaneous reactions.

We don't specifically look at by age. We do generate that data, and we have not seen a signal for the higher age patients for any of the subgroups that have been commented here; no new safety signals outside of what we see, which we expect that we've seen with IV Rituxan.

So completely comparable data with IV Rituxan, so just wanted to comment on that.

DR. DAVIES: Andrew Davies, medical oncologist in the UK. Of course, we see a whole range of ages in these disease groups; particularly

we see in the elderly population. We make no restrictions on delivery according to age, and we have given a lot of treatment to patients older than 80 and older than 90.

Our clinical experience mirrors the experience in clinical trials, and I have seen no excess of toxicity in the older population.

DR. ROTH: Okay. Courtney?

MS. PREUSSE: Courtney Preusse, Fred Hutch. I have a question regarding safety data or data surrounding the safety of rituximab subcutaneous with subsequent lines of therapy, combination therapy.

I read in Dr. Schwarsin's last slide, in the safety summary, that the safety of rituximab SC with subsequent lines of therapy is unknown. So I'm wondering if preliminary data exists or whether those who are currently administering rituximab subQ could comment on observations associated with other lines of therapy and what those lines of therapy might be, subsequent lines of therapy might be?

DR. VALENTE: With rituximab IV, I think we have to go back to the historical data in rituximab IV, which is given to patients over their lifetime with serial treatments. And we've not seen anything that tells us that that is unsafe or there's some cumulative toxicity due to the repetitive administrations of rituximab in combination with chemotherapy over their lifetime.

Because we had a PK bridging approach here, and we showed non-inferior exposure and similar exposure to those approved doses and schedules of rituximab IV, we wouldn't expect to see any issue with giving the subcutaneous rituximab over again in the relapse setting.

So we haven't studied that. These were first-line studies as Dr. Schwarsin has pointed out, but there's no reason to believe that if we gave this for the next line of therapy, that this would be an issue.

I don't know if Dr. Davies, if he has experience in that, and we'll hear from him.

DR. DAVIES: Andrew Davies, medical

oncologist from the UK. We have, indeed, delivered subcutaneous rituximab in the second and subsequent line without any -- this is the same drug. It is rituximab. There is no difference. There's no reason to suspect that it would be more toxic in subsequent settings. So we safely -- again, I don't have data to precisely, to support this, but remember, it's the same drug as we deliver IV.

DR. ROTH: Thank you.

Are there any other questions from the panel members?

(No response.)

DR. ROTH: Then maybe I can finish up with just one, and that refers to the PFS curve on SABRINA. In your hard document, it's figure 16. I don't know what slide it would be. And my question is -- my compliments to you for not overselling this in the document. But the separation of the PFS curves in the document, they start to separate at about 30 months or so.

In the document, you say that this is probably a shrinking denominator phenomenon, not a

lot of events, but is there a possibility that there's something here and whether it relates to kind of the inverse of Dr. Waldman's comments. Is it related maybe to a difference in C-trough in maintenance therapies? Is there a possibility there's really a difference in maintenance therapy and something to be interrogated going forward with the subQ arm being superior?

DR. VALENTE: When we get out to the maintenance therapy, we're definitely in a steady state, and the ratio of the subQ to the IV probably continues to remain steady. We've seen from actually the FDA's graph the geometric mean ratio over time. I think it was both for SABRINA and SAWYER. I'm going to ask Dr. Morcos to further elaborate on this question. You can see in one of the FDA graphs this over time.

DR. MORCOS: Peter Morcos, clinical pharmacologist. So in addition to investigating the relationship between rituximab exposure and safety events, we've also investigated the relationship between rituximab exposure and

efficacy endpoints, including PFS.

One analysis we did was a Cox regression assessment with exposure as a metric in it. What we determined in the majority of patients in SABRINA, so 98 percent of patients, there was no exposure-efficacy relationship. So the majority of patients are deriving clinical benefit with rituximab.

DR. ROTH: Okay. Thank you.

Any other questions?

(No response.)

Questions to Committee and Discussion

DR. ROTH: Okay. Thank you. We'll close the clarifying question section.

As it turns out, there are no registered speakers for the open public forum today, so we're going to move past that, and we'll move directly to the question and discussion proposed to the committee.

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 for this particular section.

The solitary question that will be proposed to the committee will be, is the benefit-risk favorable for the above drug product for the proposed indications in follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia?

So I'll open the floor to discussion about this particular question. First, are there any changes or questions in the way the question is formatted? Are there questions about what you'll ultimately be voting on?

(No response.)

DR. ROTH: Okay. So now we'll open it up for discussion. I would also encourage the non-voting members of the committee to participate here. When you make your comments, don't indicate your vote, but just your feelings about the information as it's been provided and any questions that remain to you. So if anyone would like to start the discussion. Go ahead.

DR. BURSTEIN: I'll ask a question I think I know the answer to. We're talking about a combination product, right? We're not talking about two elements of a generic product.

For instance, there's interest in biosimilar rituximab and other biologics, and were this drug to be on the market, would the availability of a biosimilar rituximab have any bearing on the construction or delivery of the product that we're voting upon today, I guess is what I'm wondering.

DR. ROTH: Dr. Pazdur, would you like to comment on that?

DR. PAZDUR: I don't think so, no.

DR. BURSTEIN: And in a product like this, were it on the market, is there the potential for interchangeability for the -- either component, because they're both biologics I suppose -- to be introduced into a combination product through a biosimilars program, or would that have to be done de novo because of the combination?

DR. DE CLARO: Angelo de Claro with FDA. As I indicated in the intro, this is not a biosimilar.

The terms biosimilar are interchangeable and are best reserved for -- if you're dealing with a different product that's comparing to the U.S. license reference product. As we've heard from the sponsor in their presentation, this is the same antibody.

With regards from a regulatory perspective, we're classifying this as a single-entity product that has two active components. So both rituximab and hyaluronidase would be -- our preliminary assessment, they're both active, but it's in the same vial, so there are no concerns with regards to that these would be separated out.

DR. BURSTEIN: So in other words, we're being asked to vote on the chocolate sundae. That is it's not vanilla ice cream, it's not chocolate sauce, it's the sundae --

DR. DE CLARO: Yes, it is.

DR. BURSTEIN: -- and you have to take it or leave it as it is. And if in the future there are different vanilla ice creams or chocolate sauces, that's a different discussion.

DR. DE CLARO: Correct.

DR. BURSTEIN: Correct.

(Laughter.)

DR. ROTH: I don't even know how to follow up on that.

(Laughter.)

DR. BURSTEIN: Just hungry I guess.

(Laughter.)

DR. ROTH: I hope it gets transcribed word-for-word though.

Are there any other comments about the question as proposed or in general your feelings about the discussions from today, before we move on to a vote?

(No response.)

DR. ROTH: Okay. If not, we'll move on to the voting section here.

We'll be using an electronic voting system for this meeting. Once we begin the vote, the 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're unsure of your vote, or you 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 state their vote into the record, and then please comment on the reason why you voted as you did.

So barring questions, let's proceed. So please press the button on your microphone that corresponds to your vote. You have approximately 20 seconds to vote. Please press the button firmly. If you're unsure of your vote or you wish to change, please press the corresponding button.

DR. TESH: For the record the voting result is 11, yes; no, zero; abstain, zero; no voting, zero.

DR. ROTH: 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, state the reason why you voted as you did into the record. We'll start on this side. Dr. Harralson?

DR. HARRALSON: Obviously, I voted yes.

(Laughter.)

DR. HARRALSON: It's a really good product. I guess my concern is the whole idea of the fixed dose. And not to get too personal, I have a daughter who's 4'11" and weighs less than a hundred pounds, and I'm looking at what I see as the area under the curve relative to body surface area, and there's a huge difference there.

Now I suppose it is true that we have a broad therapeutic index, so it may be okay. I just think it ought to be adjusted for smaller people, but it's a good product.

DR. ROTH: Dr. Waldman?

DR. WALDMAN: I voted yes. I thought the data package was convincing and compelling and fills an unmet medical need.

DR. KARARA: I voted yes. I agree data is

very strong and supportive of the claim.

MR. MAJKOWSKI: Paul Majkowski, patient representative. I voted yes. From the patients' perspective, when we're looking at a new therapy, one of the things that I consider is whether there is too much choice. But here, certainly we have a situation where -- with this patient preference, as much as I loved the company of my chemotherapy nurses, not having to sit in a chair for 4 hours as opposed to getting an injection is preferable. And there is no diminishment from the data in terms of efficacy or safety. So I voted yes.

MS. PREUSSE: Courtney Preusse. I also voted yes, and the motivating factor was the patient preference, and the implied association with the improved quality of life by having to spend less time in a chemo chair.

DR. SHAW: Alice Shaw. I voted yes as well. This is the same drug that we've used for two decades that has proven survival benefits. I think the pharmacology was very compelling, and there is comparable efficacy as well as safety.

DR. COLE: Bernard Cole. I voted yes. I found as mentioned already, the data very compelling, and the package, and the PK data especially. And I was feeling that the sponsor did a really good job showing results about safety and efficacy as well through multiple clinical trials, and there's just no signal whatsoever that there's any compromise in efficacy.

DR. ROTH: Bruce Roth. I voted yes. First, I'd like to compliment the sponsor on the clarity of their document and the presentation, which is not always the case, but certainly made for a compelling story.

I understand the concerns, particularly in well BSA individuals when you're talking about neutropenia that might compromise the doses of other agents that you're getting, and I think in the back of our minds, that's going to dwell for a while. But certainly the postmarketing data on a large number of patients over a large number of patients over a number of years says that while there may be a concern, it probably pertains to a

fairly small number of patients.

DR. ULDRICK: Thomas Uldrick. I voted yes. I think this is going to be a useful product in the real-world setting, and I was very impressed by the presentation of the PK data and the safety data.

DR. KLEPIN: Heidi Klepin. I voted yes for a lot of the same reasons. Data package was compelling. It's going to be a really important product for our patients. It absolutely will, I think, improve their satisfaction with the experience. And I would love to see some of the postmarketing data on the older patients in particular, but I don't have significant concerns that we can't extrapolate.

DR. BURSTEIN: Hal Burstein. Of course, also I voted yes. Most of the points have already been made. My only concerns are I think it's an absurdly high level of evidence to think about other products in a similar space here, with multiple randomized trials and extensive pharmacokinetic data. I don't know that anything less than the world's number one selling drug by

dollar would generate such enthusiasm for a similar approach, and I worry that we've set the bar for such things very high.

But having said that, as my colleagues have already said, I thought the data were almost impeccable in terms of their quality. And I particularly liked the patient preference survey. I thought that was a very nice addition. It's a nice thing to be able to ask patients how they really want to spend their time.

I personally think things like chair time, from an institutional point of view, are vastly overrated. There aren't that many practices that are so efficient that an extra 30 minutes or 60 minutes of Rituxan ruins the whole day for everybody. But listening to patients and having them say that this makes a big difference, especially for maintenance therapy, I think is quite compelling.

Adjournment

DR. ROTH: Okay. Well thank you very much. Thank you to the panel members and the members of

the agency and all the guests from the sponsor, an excellent presentation. I would remind the panel members to leave your name badge here on the table so that they might be recycled, and please take all your personal belongings as this room will be cleared at the end of the day. And meeting materials, if you wish to leave them, hard copies will be disposed of. So thank you very much.

(Whereupon, at 10:53 a.m., the meeting was adjourned.)